03-29-00

DAC / Petition # #20

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US Patent No. 5,360,800 07/741570

Issued: 1 November 1994

Inventors: Ian H. Coates, Peter C. North, and Alexander W. Oxford.

Assignee: Glaxo Group Limited

For: TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES

Re: Patent Term Extension for U.S. Patent No. 5,360,800

Asst. Commissioner of Patents
Box Patent Extension
Washington DC 20231

Sir:

Transmitted herewith is an Application for Extension of a Patent Term under 35 U.S.C. 156 with regard to U.S. Patent No. 5,360,800.

The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392. Triplicate copies of this letter are enclosed.

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Express Mail Label No. EM484297842US

Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723

Respectfully submitted,

Glaxo Wellcome Inc.

March 27, 2000

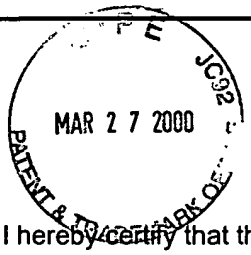
By: _____

David J. Levy, Ph. D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.

CERTIFICATE OF MAILING BY "EXPRESS MAIL" (37 CFR 1.10) Applicant(s): Coates, et al.			Docket No. NDA 21-107
Serial No. Pat. No. 5,360,800	Filing Date Granted: Nov 1, 1994	Examiner	Group Art Unit

Invention:

TETRAHYDRO-1H-PYRIDO [4,3-b] INDOL-1-ONE DERIVATIVES



I hereby certify that this **Patent Term Extension for US Patent No. 5,360,800**
(Identify type of correspondence)

is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 in an envelope addressed to: The Assistant Commissioner for Patents, Washington, D.C. 20231 on

March 27, 2000
(Date)

Rosalie M. Germano
(Typed or Printed Name of Person Mailing Correspondence)

Rosalie M. Germano
(Signature of Person Mailing Correspondence)

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US Patent No. 5,360,800

Issued: 1 November 1994

Inventors: Ian H. Coates, Peter C. North, and Alexander W. Oxford.

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Vice President and Assistant Secretary
Intellectual Property Counsel
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US Patent No. 5,360,800

Issued: 1 November 1994

Inventors: Ian H. Coates, Peter C. North, and Alexander W. Oxford.

Assignee: Glaxo Group Limited

For: TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES

Re: Patent Term Extension for U.S. Patent No. 5,360,800

Asst. Commissioner of Patents
Box Patent Extension
Washington DC 20231

Sir:

Applicant, Glaxo Wellcome Inc., a corporation of the State of North Carolina, represents that it is the Agent of Glaxo Group Limited, a corporation incorporated in England, for the purposes of filing an Application for Patent Term Extension for U.S. Patent No. 5,360,800 pursuant to the attached Declaration of David J. Levy and the Power of Attorney provided at EXHIBIT 1.

Applicant further represents, pursuant to 35 U.S.C. 156(d)(1), that Glaxo Group Limited, is the record owner and assignee of the entire right title and interest in and to Letters Patent of the United States of America No. 5,360,800 granted to Ian H. Coates, Peter C. North, and Alexander W. Oxford on 1 November 1994 for TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES by virtue of an assignment to Glaxo Group Limited dated 22 August 1988, which assignment was recorded in the United States Patent and Trademark Office on 15 September 1988 on Reel 4993, Frame 0723. See EXHIBIT 2.

Applicants further represent, pursuant to 37 C.F.R. 1.785(d), that Applicant is the holder of the regulatory approval granted by the Food and Drug Administration ("FDA") for LOTRONEX® (Alosetron hydrochloride) Tablets (hereinafter, "LOTRONEX®"). A copy of the Food and Drug Administration (FDA) Approval Letter for LOTRONEX® is attached hereto as EXHIBIT 3.

Applicant hereby submits this Application for Extension of Patent Term under 35 U.S.C. 156 by providing the following information pursuant to 37 C.F.R. 1.740. For convenience, the information contained in this application will be presented according to the format set forth in 37 C.F.R. 1.740(a).

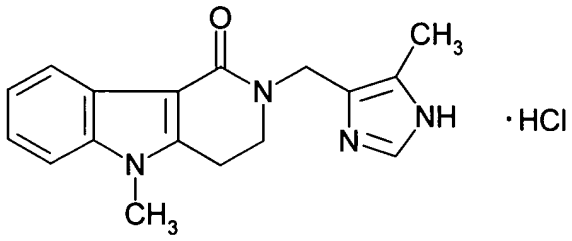
Express Mail Label No. EM484297842US

(1) This application for patent term extension is based upon the regulatory review period before the FDA, of Applicant's approved product, LOTRONEX® (alosetron hydrochloride) Tablets. The only active ingredient in LOTRONEX® Tablets is alosetron hydrochloride. A copy of the package insert approved by the FDA as part of New Drug Application 21-107 (NDA) is attached hereto as EXHIBIT 4. Identification of the approved product is provided as follows:

Chemical Name(s): 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one, hydrochloride

Molecular formula: $C_{17}H_{18}N_4O \cdot HCl$

Structural formula:



Molecular weight: 330.8

Physical Form: White to beige solid

(2) The approved product, LOTRONEX® (Alosetron hydrochloride) Tablets was subject to regulatory review under the Federal Food, Drug and Cosmetic Act, section 505 (21 U.S.C. 355). See EXHIBIT 3.

(3) LOTRONEX® Tablets received permission for commercial marketing and use under section 505 of the Federal Food, Drug and Cosmetic Act (21 U.S.C. 355) on 9 February 2000. See EXHIBIT 3.

(4) Alosetron hydrochloride, the only active ingredient in LOTRONEX® Tablets has not been previously approved for commercial marketing or use under the Federal Food Drug and Cosmetic Act, the Public Health Service Act, or the Virus-Serum-Toxin Act.

(5) This application for extension of patent term under 35 U.S.C. 156 is being submitted within the permitted 60-day period, which will expire on 9 April 2000.

(6) The complete identification of the patent for which extension of term is being sought is as follows:

U.S. Patent No.:	5,360,800
For:	TETROHYDRO-1H-PYRIDO[4,3-B]INDOL-1-ONE DERIVATIVES
Inventors:	Ian H. Coates, Peter C. North, and Alexander W. Oxford
Assignee:	Glaxo Group Limited
Issued:	1 November 1994
Expiration Date:	2 February 2010

(7) A complete copy of the patent identified in paragraph (6) above is attached hereto as EXHIBIT 5.

(8) A copy of the Terminal Disclaimer filed for U.S. Patent 5,360,800, disclaiming the portion of patent term extending beyond the expiration date of U.S. Patent 5,183,820, is attached hereto as EXHIBIT 6.

(a) A copy of the Assignment filed in U.S. Patent 5,183,820, assigning all right, title and interest in U.S. Patent 5,183,820 to Glaxo Group Limited, is attached hereto as EXHIBIT 7.

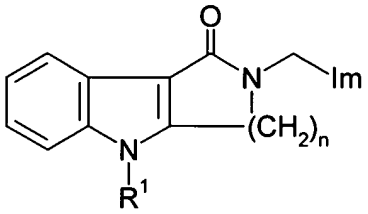
(b) No certificates of correction have issued for this patent.

(c) Copies of all receipts of all maintenance fee payments made with respect to U.S. Patent 5,360,800 are attached hereto as EXHIBIT 8.

(d) No reexamination certificate exists in respect of U.S. Patent 5,360,800.

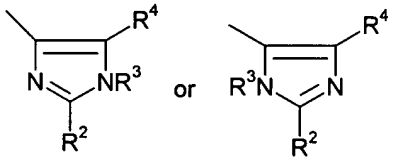
(9) United States Patent 5,360,800 claims the active ingredient, alosetron hydrochloride, in the approved product LOTRONEX® Tablets. Applicant hereinbelow lists each applicable patent claim and demonstrates the manner in which each applicable claim reads on the approved product or method of using the approved product.

(a) Claim 1 reads as follows: "A compound of formula (I)



(I)

wherein Im represents an imidazolyl group of the formula:



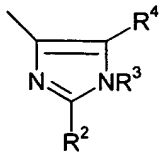
and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl;

one of the groups represented by R^2, R^3, and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6}alkyl group;

n represents 2 or 3;

or a physiologically acceptable salt or solvate thereof."

Claim 1 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where Im represents



R^1 is C_{1-6}alkyl, specifically C_1alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; R^4 is C_{1-6}alkyl, specifically C_1alkyl or methyl; and n is 2.

(b) Claim 2 reads as follows: "A compound according to claim 1 in which R^1 represents a C_{1-4}alkyl, C_{3-4}alkynyl, C_{5-6}cycloaklyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, or phenylmethoxymethyl."

Claim 2 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is a C_{1-4}alkyl, namely C_1alkyl or methyl.

(c) Claim 3 reads as follows: "A compound according to claim 1 in which R^2, R^3, and R^4 each independently represent a hydrogen atom or a C_{1-3}alkyl group."

Claim 3 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^2 is a hydrogen atom; R^3 is a hydrogen atom; and R^4 is a C_{1-3}alkyl group, specifically C_1alkyl or methyl.

(d) Claim 4 reads as follows: "A compound according to claim 1 in which R^1 represents a hydrogen atom or a C_{1-4}alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, or phenylmethoxymethyl; R^2 represents a hydrogen atom; and R^3 and R^4 each represent a hydrogen atom or a C_{1-3}alkyl group."

Claim 4 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is C_{1-4}alkyl, specifically C_1alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; and R^4 is C_{1-3}alkyl, specifically C_1alkyl or methyl.

(e) Claim 5 reads as follows: "A compound according to claim 1 in which R^1 represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, or benzyl; R^2 and R^3 each represent a hydrogen atom; and R^4 represents a methyl group."

Claim 5 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula

I, where R^1 is methyl; R^2 and R^3 each represent a hydrogen atom; and R^4 is a methyl group.

(f) Claim 6 reads as follow: "A compound according to claim 4 in which n represents 2."

Claim 6 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is C_{1-4}alkyl, specifically C_1alkyl or methyl; R^2 is a hydrogen atom; R^3 is a hydrogen atom; R^4 is C_{1-3}alkyl, specifically C_1alkyl or methyl; and n represents 2.

(g) Claim 7 reads as follows: "A compound according to claim 5 in which n represents 2."

Claim 7 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of a compound according to formula I, where R^1 is methyl; R^2 and R^3 each represent a hydrogen atom; R^4 is a methyl group; and n represents 2.

(h) Claim 8 reads as follows: "2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one; or a physiologically acceptable salt or solvate thereof."

Claim 8 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(i) Claim 10 reads as follows: "A compound according to claim 1 in the form of a hydrochloride, hydrobromide, sulphate, alkylsulphonate, arylsulphonate, phosphate, acetate, citrate, succinate, tartrate, fumarate or maleate salt."

Claim 10 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a hydrochloride salt form of the compound according to formula I of claim 1 (*see* item 9(a) *supra*).

(j) Claim 11 reads as follows: "The compound of claim 8 in the form of a hydrochloride salt."

Claim 11 reads on the approved product, LOTRONEX® Tablets, because the active ingredient of the approved product, alosetron hydrochloride, is a hydrochloride salt of the compound according to claim 8 (*see* item 9(h) *supra*).

(k) Claim 13 reads as follows: "A pharmaceutical composition which comprises an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient."

Claim 13 reads on the approved product, LOTRONEX® Tablets, because the approved product is a pharmaceutical composition which contains the active ingredient alosetron hydrochloride, which is a compound according to claim 1 (*see* item 9(a) *supra*), together with lactose anhydrous, magnesium stearate, microcrystalline cellulose, and pregelatinized starch, which are pharmaceutically acceptable carriers.

(l) Claim 14 reads as follows: "A pharmaceutical composition according to claim 13 in a form adapted for oral or parenteral administration."

Claim 14 reads on the approved product, LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (*see* item 9(k) *supra*) which contains the active ingredient alosetron hydrochloride in a form adapted for oral administration.

(m) Claim 15 reads as follows: "A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 15 reads on the approved product LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (*see* item 9(k) *supra*) which contains the active ingredient alosetron hydrochloride, which is a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(n) Claim 16 reads as follows: "A pharmaceutical composition according to claim 13, wherein the active ingredient is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 16 reads on the approved product LOTRONEX® Tablets, because the approved product is a pharmaceutical composition according to claim 13 (*see* item 9(k) *supra*) containing the active ingredient alosetron hydrochloride, which is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(o) Claim 17 reads as follows: "A method of treating a condition which is ameliorated by antagonism of $5HT_3$ receptors which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof to relieve said condition."

Claim 17 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of $5HT_3$ receptors, namely irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of a compound of formula (I) as defined in claim 1 (*see* item 9(a) *supra*).

(p) Claim 18 reads as follows: "A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 18 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of $5HT_3$ receptors, namely irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(q) Claim 19 reads as follows: "A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 19 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of a condition which is ameliorated by antagonism of $5HT_3$ receptors, namely irritable bowel syndrome

in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(r) Claim 27 reads as follows: "A method according to claim 17 for the treatment of irritable bowel syndrome."

Claim 27 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt of a compound of formula (I) as defined in claim 1 (*see* item 9(a) *supra*).

(s) Claim 28 reads as follows: "A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof."

Claim 28 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of a physiologically acceptable salt, namely a hydrochloride salt, of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one.

(t) Claim 29 reads as follows: "A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride."

Claim 29 reads on the method of using the approved product because LOTRONEX® Tablets are indicated for the treatment of irritable bowel syndrome, specifically treatment of irritable bowel syndrome in females whose predominant bowel symptom is diarrhea as labeled, through administration of an effective amount of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

(10) The relevant dates and information pursuant to 35 U.S.C 156(g) necessary to enable the Secretary of Health and Human Resources to determine the applicable regulatory review period are as follows:

(a) Effective Dates and Numbers of the INDs

The first Investigational New Drug Application ("IND") for alosetron hydrochloride became effective 10 May 1990; it was designated IND No. 34,672 (Alosetron Hydrochloride Tablets for Treatment of Cognition Disorders). See EXHIBIT 9A.

The second IND for alosetron hydrochloride became effective 11 April 1992; it was designated IND No. 39,083 (Alosetron Hydrochloride Tablets for Treatment of Schizophrenia). See EXHIBIT 9B.

The third IND for alosetron hydrochloride became effective 25 May 1994; it was designated IND No. 45,128 (Alosetron Hydrochloride for the Treatment of Carcinoid Diarrhea). See EXHIBIT 9C.

The fourth IND for alosetron hydrochloride became effective 6 September 1995; it was designated IND No. 48,487 (Alosetron Hydrochloride Tablets for Treatment of Irritable Bowel Syndrome). See EXHIBIT 9E.

The fifth IND for alosetron hydrochloride became effective 23 December 1999; it was designated IND No. 59,496 (Alosetron Hydrochloride Oral Solution). See EXHIBIT 9G.

Each of these IND's is discussed in more detail in Section 13, *infra*.

(b) Issue Date of Patent

US Patent No. 5,360,800 issued 1 November 1994 and claims a new drug, drug product, and methods of using the drug. See EXHIBIT 5.

(c) Submission Date and Number of NDA

The NDA for LOTRONEX® Tablets was submitted on 30 June 1999 and was designated NDA No. 21-107. See EXHIBIT 9F.

(d) Approval Date of NDA

NDA No. 21-107 for LOTRONEX® Tablets was approved by the FDA on 9 February 2000. See EXHIBIT 3.

(11) A brief description of the significant activities undertaken by Applicant during both the IND and NDA regulatory periods is presented in a chronological form and is attached hereto as EXHIBIT 9 (including EXHIBITS 9-A through 9-G), "Due Diligence Log".

(a) The Due Diligence Log reflects significant communications with FDA during regulatory periods. Such communications include, but are not limited to: submission of preclinical reports; registration of clinical protocols and amendments thereof; registration of clinical investigators and amendments thereof; submission of adverse event reports; submission of IND Annual Reports, etc.

(b) Periods between such communications enumerated in the Due Diligence Log reflect Applicant's diligent undertaking of the necessary clinical studies and other activities required by the FDA in order to obtain approval for Applicant's product.

(12) Applicant is of the opinion that U.S. Patent 5,360,800 is eligible for a 1076-day extension which is not subject to the 14-year limitation under 35 U.S.C. 156(c)(3). See EXHIBIT 10.

(a) Applicant has satisfied the eligibility criteria necessary to obtain a patent term extension pursuant to 35 U.S.C. 156.

(1) 35 U.S.C. 156(a)
U.S. Patent No. 5,360,800 claims a drug product and a method of using a drug product.

(2) 35 U.S.C. 156(a)(1)
The term of U.S. Patent No. 5,360,800 has not yet expired before submission of this application.

(3) 35 U.S.C. 156(a)(2)
The term of U.S. Patent No. 5,360,800 has never been extended.

(4) 35 U.S.C. 156(a)(3)
The application for extension is submitted by the agent for the owner of record in accordance with the requirements of 35 U.S.C. 156(d) and 37 C.F.R. 1.710 *et seq.*

(5) 35 U.S.C. 156(a)(4)
The approved product, LOTRONEX® Tablets, has been subject to a regulatory review period before its commercial marketing or use.

(6) 35 U.S.C. 156(a)(5)(A)
The commercial marketing or use of the approved product, LOTRONEX® Tablets, after the regulatory review period is the first permitted commercial marketing or use of the approved product under the provisions under which such regulatory review period occurred.

(b) Applicant herewith claims a patent term extension of 1076 days, which is not limited by the 14-year limitation under 35 U.S.C. 156(c)(3), for U.S. Patent No. 5,360,800 pursuant to U.S.C. 156(g) as follows:

(1) One half the IND regulatory review period for the approved product beginning 1 Nov 1994 (the IND period occurring after the date of issuance of U.S. Patent No. 5,360,800) and ending on 29 June 1999 (one day prior to the date on which the NDA for the approved product was initially submitted).

(2) The full term of the NDA regulatory review period commencing 30 June 1999 (the date NDA 21-107 for the approved product was originally submitted) and ending on 9 February 2000 (the date on which NDA 21-107 was approved).

(3) The sum of Items 12(b)(1) and 12(b)(2) *supra* is equal to 1076 days. See EXHIBIT 10.

(c) Applicant herewith claims an extension expiry date of **13 January 2013** for U.S. Patent 5,360,800 pursuant to 35 U.S.C. 156(c)(3).

(1) The expiration of U.S. Patent 5,360,800, by virtue of the terminal disclaimer, is 2 February 2010.

(2) Extending the 2 February 2010 date by 1076 days would result in an expiration date of **13 January 2013**. See EXHIBIT 10.

(3) 35 U.S.C. 156(c)(3) requires that term extensions if necessary be reduced in order to limit the expiration date of a patent receiving term extension to 14 years from the date of NDA approval. The expiration date of U.S. Patent 5,360,800 is therefore not limited by the provisions of 35 U.S.C. 156(c)(3). See EXHIBIT 10.

(13) The Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and the Secretary of Health and Human Services any information which is material to any determinations to be made relative to the application for extension. The following information is provided for consideration.

(a) Applicant filed the first IND for alosetron hydrochloride tablets on 10 April 1990 (for the treatment of cognition disorders); it was designated IND No. 34,672. IND No. 34,672 was received by the FDA on 10 April 1990. The effective date of IND No. 34,672 is therefore 10 May 1990, pursuant to 21 CFR 312.40(b). IND No. 34,672 was placed on clinical hold on 30 July 1991 by the Division of Neuropharmacological Drug Products. A request for inactive status for IND No. 34,672 was filed on 9 June 1994 and was acknowledged by the FDA on 9 July 1994. To Applicants' knowledge, IND No. 34,672 has not been terminated, and was pending as of the date of submission of NDA 21-107. See EXHIBIT 9A.

(b) Applicant filed the second IND for alosetron hydrochloride tablets on 11 March 1992 (for the treatment of schizophrenia); it was designated IND No. 39,083. IND No. 39,083 was received by the FDA on 12 March 1992. The effective date of IND No. 39,083 is therefore 11 April 1992, pursuant to 21 CFR 312.40(b). A request for inactive status for IND No. 39,083 was filed on 8 June 1994. To Applicants' knowledge, IND No. 39,083 has not been terminated, and was pending as of the date of the submission of NDA 21-107. See EXHIBIT 9B.

(c) The third IND for alosetron hydrochloride tablets -- IND No. 45,128 -- was filed on 22 April 1994, was received by FDA on 25 April 1994, and became effective 25 May 1994, pursuant to 21 CFR 312.40(b). See EXHIBIT 9C. The first U.S. studies of alosetron hydrochloride tablets for a gastrointestinal treatment use, namely for the treatment of carcinoid diarrhea, were conducted under IND No. 45,128. Specifically, the studies conducted under IND No. 45,128 were as follows: 1) An Effectiveness, Three Dose Study Of Alosetron In The Medium-Term Treatment Of Patients With Carcinoid Diarrhea, and 2) An Open-Label, Single Dose Trial Of Alosetron In The Treatment Of Patients With Carcinoid Diarrhea. Applicant contracted with Dr. Michael Camilleri, acting through the Mayo Foundation for Medical Education and Research ("Mayo"), to conduct these studies, and it was Dr. Camilleri who filed the IND.

Applicant collaborated closely on IND No. 45,128 and ultimately relied on the studies conducted under it in support of approval for NDA No. 21-107. Applicant's active role and deep vested interest in IND No. 45,128 are illustrated by the following:

(i) *Full financial responsibility*: Applicant bore a contractual obligation to finance the studies conducted under IND No. 45,128, at considerable expense.

(ii) *Supply of study drug*: Applicant manufactured and supplied all alosetron hydrochloride tablets administered to patients under IND No. 45,128.

(iii) *Substantiation and informational support of the IND filing*: Applicant's earlier clinical and pre-clinical experience with alosetron hydrochloride tablets, as well as Applicant's information concerning chemistry, manufacturing, and controls, were indispensable elements of IND No. 45,128, without which studies could not have proceeded. IND No. 45,128 incorporated Applicant's earlier INDs for alosetron hydrochloride by reference (see below for more information about the earlier INDs), and otherwise relied extensively upon Applicant's previous drug development and manufacturing history with alosetron hydrochloride.

(iv) *Guidance and Technical Assistance in preparation of IND filing*: Applicant provided guidance and technical assistance in meeting the FDA requirements in both the compilation of IND No. 45,128 and in meeting reporting obligations, as requested by Dr. Camilleri.

(v) *Rights to full use of study results*: Applicant secured a contractual right to full use of the results of the studies conducted under IND No. 45,128. As provided by the governing contract, "GLAXO and MAYO agree that ... GLAXO shall have an exclusive License to use any and all [study] results in any way deemed by it to be necessary or advisable, either directly or through agents or otherwise, without payment of any compensation to MAYO for same."

(vi) *Rights to rely on study results in filings with FDA*: Applicant secured a contractual right to rely on the results of the studies conducted under IND No. 45,128 to advance alosetron hydrochloride to approval. As provided by the governing contract, "MAYO agrees to approve GLAXO's reliance on such Study results in any future filings with the Food and Drug Administration ("FDA") for Alosetron."

(vii) *Rights to assistance in proceedings before FDA*: Applicant secured a contractual right to assistance from Dr. Camilleri and Mayo in regulatory filings and proceedings, such as the filing of an NDA. As provided in the governing contract, "MAYO will make reasonable efforts to give GLAXO assistance and cooperation required by GLAXO related to the study in connection with informal presentations, discussions, submissions, administrative hearings or court proceedings involving the FDA or other federal or state agencies."

(viii) *Actual use and reliance on the study results in support of NDA 21-107*: NDA 21-107 for Alosetron Hydrochloride Tablets refers to IND No. 45,128 and reports data generated in the studies conducted by Dr. Camilleri. Moroever, Dr. Camilleri appeared on behalf of Applicant at

the meeting of the Gastrointestinal Drugs Advisory Committee on 16 November 1999, at which the panel reviewed NDA 21-107. At the meeting, Dr. Camilleri discussed data generated under IND No. 45,128. A transcript of Dr. Camilleri's remarks is attached as EXHIBIT 9D.

(d) Applicant filed the fourth IND for alosetron hydrochloride tablets on 4 August 1995 (for the treatment of irritable bowel syndrome); it was designated IND No. 48,487. IND No. 48,487 was received by the FDA on 7 August 1995. The effective date of IND No. 48,487 is therefore 6 September 1995, pursuant to 21 CFR 312.40(b). Phase III clinical trials supporting approval of NDA No. 21-107 were conducted under IND No. 48,487. See EXHIBIT 9E.

(e) Applicant filed a fifth IND for alosetron hydrochloride on 17 December 1999 (for Alosetron Hydrochloride Oral Solution); it was designated IND No. 59,496. The effective date of IND No. 59,496 was 23 December 1999, the FDA having waived the 30-day period under 21 CFR 312.40(b). See EXHIBIT 9G.

(f) Applicants filed an NDA for LOTRONEX® (alosetron hydrochloride) Tablets on 30 June 1999; it was designated NDA No. 21-107. See EXHIBIT 9F. The NDA contains data from and references IND Nos. 34,672, 39,083, 45,128 and 48,487.

(g) Applicants' NDA was approved on 9 February 2000. See EXHIBIT 3.

(14) The Commissioner of Patent and Trademarks is hereby authorized to charge deposit account number 07-1392 in the amount of $1,120.00 for receiving and acting upon this application for extension of term. In the event the actual fees due in connection with Applicant's application for patent term extension differ from the amount specified above, the Commissioner is hereby authorized to credit any overpayment or charge any underpayment to Applicants' deposit account number 07-1392.

(15) Inquiries and correspondences relating to this application for patent term extension are to be directed to:

David J. Levy, Ph.D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723

(16) A duplicate of the application papers, certified as such, is attached hereto.

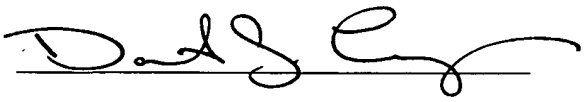
(17) Submitted herewith is a Declaration by David J. Levy, Ph.D., Patent Counsel for Glaxo Wellcome Inc., which meets the criteria set forth in 37 CFR 1.740(b), and includes a Rule 3.73(b) certification on behalf of Glaxo Group Limited, which establishes the right of Glaxo Group Limited, as assignee, to take action in the Patent and Trademark Office in connection with this patent, including the naming of Applicant as its agent for purposes of filing this application, and grants power of attorney to the named registered patent attorneys.

The undersigned hereby certifies that this Application for Extension of Patent Term Under 35 U.S.C. 156, including Exhibits 1-10 and supporting papers, is being submitted as duplicate originals.

Respectfully submitted,

Glaxo Wellcome Inc.

3/27/2000

By: 

David J. Levy, Ph. D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.

Express Mail Label No. EM484297842US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re: US Patent No. 5,360,800

Issued: November 1, 1994

Inventors: Ian H. Coates, Peter C. North, and Alexander W. Oxford.

Assignee: Glaxo Group Limited

For: TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES

Asst. Commissioner of Patents
Box Patent Extension
Washington, DC 20231

DECLARATION OF DAVID J. LEVY, PH.D. UNDER 37 C.F.R. 1.740(b)

CERTIFICATION UNDER 37 C.F.R. 3.73(b)

POWER OF ATTORNEY

DESIGNATION OF GLAXO WELLCOME INC. AS AGENT

Sir:

I, David J. Levy, residing in Wake Forest, North Carolina, declare as follows:

(1) I submit this declaration in connection with the Application for Patent Term Extension for US Patent No. 5,360,800 (hereinafter "Application"), which is submitted concurrently herewith.

(2) Glaxo Group Limited has, by virtue of the Power of Attorney provided at EXHIBIT 1 of the Application, authorized me to perform acts in connection with letters patent and other Intellectual Property Rights.

(3) Pursuant to 37 C.F.R. § 3.73(b) and 35 U.S.C. § 156(d)(1), Glaxo Group Limited is the record owner and assignee of the entire right title and interest in and to US Patent No. 5,360,800 granted to Ian H. Coates, Peter C. North, and Alexander W. Oxford for TETRAHYDRO-1H-PYRIDO[4,3-b]INDOL-1-ONE DERIVATIVES by virtue of assignment to Glaxo Group Limited Recorded in the United States Patent and Trademark Office on 15 September 1988, Reel 4993, Frame 0723.

Express Mail Label No. EM484297842US

(4) I have reviewed the evidentiary documents for the aforesaid chain of title and hereby certify pursuant to 37 C.F.R. § 3.73(b) that, to the best of my knowledge and belief, title is in the assignee, Glaxo Group Limited by virtue of the assignment noted in paragraph (3).

(5) Glaxo Group Limited herein issues general authority to the following attorney(s) and/or agent(s), each of Glaxo Wellcome Inc., to prosecute this Application and transact all business in the US Patent and Trademark Office connected therewith.

Charles E. Dadswell	Reg. No. 35,851
Robert H. Brink	Reg. No. 36,094
Frank P. Grassler	Reg. No. 31,164
Lorie Ann Morgan	Reg. No. 38,181
James P. Riek	Reg. No. 39,009
Virginia C. Bennett	Reg. No. 37,092
Karen L. Prus	Reg. No. 39,337
Elizabeth Selby	Reg. No. 38,298
Christopher P. Rogers	Reg. No. 36,334
John Lemanowicz	Reg. No. 37,380
Bonnie Deppenbrock	Reg. No. 28,209

(6) Glaxo Group Limited does hereby make, constitute and appoint Glaxo Wellcome Inc. organized under the laws of North Carolina, having their principal place of business at Five Moore Drive, Research Triangle Park, North Carolina 27709, United States of America as its special, true and lawful agent for the limited purpose of preparing and filing with the US Patent and Trademark Office an Application for Extension of Patent Term pursuant to 35 U.S.C. § 156(in respect of US Patent No. 5,360,800), and prosecuting said Application; and to do and perform each and every act in connection with the above-stated purpose which Glaxo Wellcome Inc. deems necessary or desirable.

(7) I make this declaration pursuant to the attached Power of Attorney, having general authority to act on behalf of Glaxo Group Limited in patent matters, and as Vice President and Assistant Secretary, Intellectual Property Counsel for Glaxo Wellcome Inc., having general authority to act on behalf of Glaxo Wellcome Inc. in patent matters.

(8) I am a patent attorney authorized to practice before the United States Patent and Trademark Office; my registration number is 27,655.

(9) I have reviewed and understand the contents of the Application submitted herewith on behalf of Glaxo Wellcome Inc. (agent for Glaxo Group Limited), requesting a 1076-day extension of the term of US Patent No. 5,360,800.

(10) I believe that US Patent No 5,360,800 is subject to extension pursuant to 37 C.F.R. §1.710.

(11) I believe that a 1076-day extension of the term of US Patent No. 5,360,800 is justified under 35 U.S.C. §156 and the applicable regulations.

(12) I believe that US Patent No. 5,360,800, for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 CFR 1.720.

(13) Any inquiries and correspondence relating to this Application for Patent Term Extension of US Patent No. 5,360,800 are to be directed to:

David J. Levy, Ph.D.
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
(919) 483-2723
fax: (919) 483-7988

I declare further that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent 5,360,800

MARCH 27, 2000

David J. Levy, Ph.D.
Registration No. 27,655
Vice President and Assistant Secretary
Intellectual Property Counsel
Glaxo Wellcome Inc.
Five Moore Drive
Research Triangle Park, NC 27709

Date:

Express Mail Label No. EM484297842US

EXHIBIT 1

General Power of Attorney from

Glaxo Group Limited to David J. Levy

Express Mail Label
No. EM484297842US

POWER OF ATTORNEY

BY THIS POWER OF ATTORNEY given this day of 18 June one thousand nine hundred and ninety seven GLAXO GROUP LIMITED a company incorporated in England (Registration No. 305979) and having its registered office at Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (hereinafter called "the Company"), HEREBY appoints Mr DAVID LEVY of Glaxo Wellcome Inc. five Moore Drive, P.O. Box 13398, Research Triangle Park, North Carolina 27709, USA to be its true and lawful agent and attorney (hereinafter called "the Attorney") on behalf and in the name of the Company or otherwise to do perform exercise or execute or concur with any other person or persons in doing performing or exercising in or for any country or countries or jurisdiction in any part of the world all or any of the following powers: acts, deeds and things in connection with letters patent, utility models, copyrights, trade mark registrations, trade marks, trade names, trade dress, logos, design rights, designs and all rights analogous thereto and all applications therefor and any other forms whatsoever of intellectual property rights, including know-how, all of which are hereinafter called "Intellectual Property Rights"; that is to say:

1. In any country or countries or jurisdiction in any part of the world to make application or cause application to be made for the grant or issue or transfer to the Company or registration in its name of Intellectual Property Rights and to take all steps necessary for the same to be prosecuted, maintained, withdrawn, renewed, enforced, defended or extended

2. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments or assurances to the Company of or under any Intellectual Property Rights or the right to and interest in any inventions to be the subject of Intellectual Property Rights for the purpose of fully and effectually vesting and transferring the same in and to the Company

3. As the act and deed of the Company to sign, seal, deliver and execute all or any assignments, assurances, licences or sub-licences from the Company of or under any Intellectual Property Rights or the right to and interest in any invention to be the subject of Intellectual Property Rights, for the purpose of fully and effectually vesting transferring or granting the same in and to any entity, whether in the United Kingdom or elsewhere, which is directly or indirectly owned or controlled by Glaxo Wellcome plc in so far as such documents can be executed without the Company's seal being affixed thereto.

For purposes of this Power of Attorney, the terms "entity" means, and includes, any person, firm or company or group of persons or unincorporated body; and "ownership" or "control" denotes the ownership or control of fifty per cent (50%) or more of the equity conferring voting rights and / or the ability otherwise to direct the business affairs of an entity.

4. To give undertakings or assurances to third parties and to any Trade Mark Registry or other official intellectual property agency or governmental department or otherwise responsible for the registration or protection of trade marks, trade names, trade dress, logos, design rights or designs for the purpose of best protecting or ensuring the co-existence of the Company's rights to trade marks, trade names, trade dress, logos, design rights or designs

5. To commence, prosecute and defend any proceedings or applications whether judicial or extra judicial relating to Intellectual Property Rights and to maintain, withdraw or settle the same

6. For and in connection with any Intellectual Property Rights to sign, seal, deliver and execute any power of attorney or other deed or document authorising any agent, including patent and trademark agents and attorneys, to act on behalf of the Company

7. To apply for the registration, amendment or cancellation of user rights in respect of any trade mark or trade name

8. To act in regard to all official communications which may now or hereafter be addressed to the Attorney relating to Intellectual Property Rights or the renewal thereof in such manner that the Attorney may be recognised as the authorised agent of the Company in all proceedings relating thereto

9. For all or any of the purposes contained herein as the act and deed of the Company to sign, seal, deliver, execute and do all such deeds, agreements, instruments and acts as shall be requisite or may be deemed proper for or in relation to the said purposes

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorney or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY RATIFIES and confirms and agrees to ratify and confirm all and whatsoever the Attorney or any person, persons, firm or company appointed by them shall lawfully do or have done by virtue of the authorities herein contained

AND THE COMPANY HEREBY DECLARES that all instruments executed under and by virtue of this Power shall be as valid and effectual as if sealed by the Common Seal of the Company

AND THE COMPANY FURTHER DECLARES that this power is in substitution for and shall revoke all previous powers of attorney granted by the Company to the Attorney to do any of the acts and things hereby authorised to be done or remaining unrevoked: PROVIDED THAT nothing herein contained shall affect the validity of any act or thing done by the Attorney by virtue thereof before the execution of this power

IN WITNESS whereof GLAXO GROUP LIMITED has caused its Common Seal to be hereunto affixed the day and year first before written

The COMMON SEAL of)
GLAXO GROUP LIMITED)
was hereunto affixed)
in the presence of:)

DIRECTOR Jeremy Strachan

~~DIRECTOR~~ / ~~SECRETARY~~ / ASSISTANT SECRETARY
Simon Bicknell

EXHIBIT 2

Assignment to Glaxo Group Limited of Application for Letters Patent of United States Patent Application No. 07/239,626

U.S. Patent No. 5,360,800

Express Mail Label No. EM484297842US

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER
OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

TO: BACON & THOMAS
625 SLATERS LA.,
4TH FLOOR
ALEXANDRIA, VA 22314

UNITED STATES PATENT AND TRADEMARK OFFICE
NOTICE OF RECORDATION OF ASSIGNMENT DOCUMENT

THE ENCLOSED DOCUMENT HAS BEEN RECORDED BY THE ASSIGNMENT DIVISION OF THE U.S. PATENT AND TRADEMARK OFFICE. A COMPLETE MICROFILM COPY IS AVAILABLE AT THE U.S. PATENT AND TRADEMARK OFFICE ON THE REEL AND FRAME NUMBER REFERENCED BELOW. A DIGEST OF THE DOCUMENT HAS ALSO BEEN MADE AND APPEARS IN THE OFFICE'S RECORDS AS SHOWN:

ASSIGNOR: 001 COATES, IAN H.	DOC DATE: 08/22/88
ASSIGNOR: 002 NORTH, PETER C.	DOC DATE: 08/22/88
ASSIGNOR: 003 OXFORD, ALEXANDER W.	DOC DATE: 08/22/88

RECORDATION DATE: 09/15/88 NUMBER OF PAGES 003 REEL/FRAME 4993/0723

DIGEST: ASSIGNMENT OF ASSIGNORS INTEREST

ASSIGNEE: 501 GLAXO GROUP LIMITED, CLARGES HOUSE, 6/12 CLARGES ST., LONDON, W1Y 8DH, ENGLAND, A BRITISH CO.

SERIAL NUMBER	7-239626	FILING DATE	09/02/88
PATENT NUMBER		ISSUE DATE	00/00/00

TITLE OF INVENTION: LACTAM DERIVATIVES

INVENTOR: 001 COATES, IAN H.
INVENTOR: 002 NORTH, PETER C.
INVENTOR: 003 OXFORD, ALEXANDER W.

A S S I G N M E N T

For good and valuable considerations, the receipt and sufficiency of which is hereby acknowledged, WE

Ian Harold Coates, 20 Mandeville Road, Hertford, Hertfordshire, England.

Peter Charles North, 60 Downlands, Royston, Hertfordshire, SG8 5BY, England.

Alexander William Oxford, 60 Green Drift, Royston, Hertfordshire, England.

do hereby sell, assign, convey and set over to our assignees,

of, Glaxo Group Limited, a British Company, of Clarges House, 6/12 Clarges Street, London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled.

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, executed on even date herewith, and in and to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor, and we do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said U.S. application to our assignee as the beneficial owner thereof;
this assignment being executed on

IN WITNESS WHEREOF, we have hereunto set our hand and seal this 22nd day of August 1988

RECORDED
PATENT & TRADEMARK OFFICE

SEP 15 88

COMMISSIONER OF PATENTS
AND TRADEMARKS OFFICE

Ian Harold Coates (L.S)
Ian Harold Coates

Peter Charles North (L.S)
Peter Charles North

Alexander William Oxford (L.S)
Alexander William Oxford

(L.S)

REEL 4903 FRAME 725

SN339
USA

UNITED KINGDOM OF GREAT BRITAIN)
CITY OF LONDON E N G L A N D) SS.

DE PINNA, SCORER & JOHN VENN
NOTARIES PUBLIC
3, ALBEMARLE STREET, LONDON W1X 3HF.
TEL: 01-409 3188
TELEX: 8951242
FAX: 01-491 7302
Groups 2&3
15 RUE DE MARIGNAN, PARIS 75008
TEL: 43 59 2617
TELEX: 640383F

I, RICHARD GRAHAM ROSSER, of the City of London, Notary Public duly admitted and sworn practising in the said City,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures "Ian Harold Coates" "Peter Charles North" and "Alexander William Oxford" set and subscribed at foot of the hereunto annexed Assignment are in each case genuine, the same having been subscribed thereto by IAN HAROLD COATES, PETER CHARLES NORTH and ALEXANDER WILLIAM OXFORD, whose identities I attest.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the City of London aforesaid, this twenty-fourth day of August One thousand nine hundred and eighty-eight.

APOSTILLE

(Hague Convention of 5 October 1961/Convention de La Haye du 5 octobre 1961)

1. Country: United Kingdom of Great Britain and Northern Ireland.
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document/Le présent acte public

2. has been signed by
a été signé par R. G. ROSSER

3. acting in the capacity of
agissant en qualité de NOTARY PUBLIC

4. bears the seal/stamp of
est revêtu du sceau/timbre de THE SAID NOTARY PUBLIC

Certified/Attesté

5. at London/à Londres

6. the/le 25 AUG 1988

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs/
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth

8. Number/sous No F 049987

9. Stamp:
timbre:

FOREIGN AND COMMONWEALTH OFFICE
DIEU ET MON DROIT
LONDON

10. Signature: B. W. GARD

For the Secretary of State/Pour le Secrétaire d'Etat

REEL 4993 FRAME 724

ASSIGNMENT

For good and valuable considerations, the receipt and sufficiency of which is hereby acknowledged, WE

Ian Harold Coates, 20 Mandeville Road, Hertford, Hertfordshire, England.

Peter Charles North, 60 Downlands, Royston, Hertfordshire, SG8 5BY, England.

Alexander William Oxford, 60 Green Drift, Royston, Hertfordshire, England.

do hereby sell, assign, convey and set over to our assignees,

of, Glaxo Group Limited, a British Company, of Clarges House, 6/12 Clarges Street, London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled.

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, executed on even date herewith, and in and to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor, and we do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said U.S. application to our assignee as the beneficial owner thereof; this assignment being executed on

IN WITNESS WHEREOF, we have hereunto set our hand and seal this 22nd day of August 1988

RECORDED
PATENT & TRADEMARK OFFICE
SEP 15 88
COMMISSIONER OF PATENTS
AND TRADEMARKS OFFICE

Ian Harold Coates (L.S)
Ian Harold Coates

Peter Charles North (L.S)
Peter Charles North

Alexander William Oxford (L.S)
Alexander William Oxford

(L.S)

EXHIBIT 3

FDA Approval Letter for LOTRONEX®

(Alosetron hydrochloride) Tablets

NDA21-107

Express Mail Label
No. EM484297842US

Food and Drug Administration
Division of Gastrointestinal and
Coagulation Drug Products
Document Control Room 6B-24
5600 Fisher's Lane
Rockville, MD 20857
Phone: 301-827-7310
Fax: 301-443-9285

Fax

To:	Mark Baumgartner	**From:**	Paul E. Levine, Jr
Fax:	919-483-5063	**Date:**	February 9, 2000
Phone:	919-486-3073	**Pages:**	4 (INCLUDING COVER PAGE)
Re:	Approval Letter, NDA 21-107	**CC:**	

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** X **Please Reply** ☐ **Please Recycle**

Comments: Please call to verify receipt of this fax

Please note that a copy of the approved labeling is not included in this fax. If a faxed copy is required, please notify me and one will be provided.

CONGRATULATIONS!

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

NDA 21-107

Glaxo Wellcome Inc.
Attention: Mark Baumgartner, RPh
Product Director, Regulatory Affairs
Five Moore Drive, P.O. Box 13398
Research Triangle Park, NC 27709

FEB 9 2000

Dear Mr. Baumgartner:

Please refer to your new drug application (NDA) dated June 29, 1999, received June 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lotronex (alosetron hydrochloride) Tablets.

We acknowledge receipt of your submissions dated August 10, 20, 23, 25, 27, and 30; September 1, 2, 3, 10, 13, 14, 15, 17, 20, 21, 22, and 24; October 15, 25, 27, and 29; November 2, 12, 15, 19, and 30; December 1, 6, 7, and 22, 1999; and January 13, 17, and 21; February 7, and 8, 2000.

This new drug application provides for the use of Lotronex (alosetron hydrochloride) Tablets, 1 mg, for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea. The safety and effectiveness of Lotronex in men have not been established.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert and patient package insert submitted February 8, 2000, immediate container and carton labels submitted December 6, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 21-107." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submissions dated December 22, 1999 and January 24, 2000. These commitments, along with any completion dates agreed upon, are listed below.

Conduct the following studies:

1. A large, long-term (1 year) population risk trial to assess the incidence of colitis in patients receiving alosetron.

2. A study to assess efficacy and safety in men with Irritable Bowel Syndrome.

3. In vitro assessment of alosetron or metabolites on cultured endothelial cell integrity. One possible model could assess whether the drug or metabolites could affect extracellular matrix synthesis and/or could induce apoptosis of endothelial cells of restricted lineage.

4. Additional studies to clarify the metabolism and disposition of alosetron in vivo. Specific issues that should be addressed include the formation of n-desmethyl-alosetron and its metabolites, especially in Asians, and identification of the unidentified circulating metabolites from the mass balance study.

5. A pharmacokinetic study in subjects with hepatic impairment. In addition to alosetron kinetics, metabolite kinetic data should also be examined.

6. In vitro pharmacology, drug metabolism, and drug interaction studies. These should include $5HT_3$ receptor affinities for any circulating or major metabolites (including conjugates), identification of P450 isozymes responsible for the formation of specific metabolites, plus the effect of alosetron and its metabolites on N-acetyltransferase 1 (NAT1), monoamine oxidases, and P450 isozymes, as appropriate.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.82(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to

contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632)(21 CFR 314.55 (or 601.27)). FDA is deferring submission of the pediatric assessments of safety and effectiveness that may be required under these regulations at this time since you have already indicated your intent, with your November 5 and December 20, 1999 Proposed Pediatric Study Requests, to pursue additional marketing exclusivity under the term of section 505A of FDAMA. These submissions are currently under review.

Submission of pediatric studies before you receive a Written Request may not fulfill the requirements for additional exclusivity. Please note that satisfaction of the requirements of 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

Victor F.C. Raczkowski 2/9/00

Victor F.C. Raczkowski, M.D., M.Sc.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

EXHIBIT 4

Approved Product Information / Package Insert for

LOTRONEX® (Alosetron hydrochloride) Tablets

NDA 21-107

Express Mail Label
No. EM484297842US

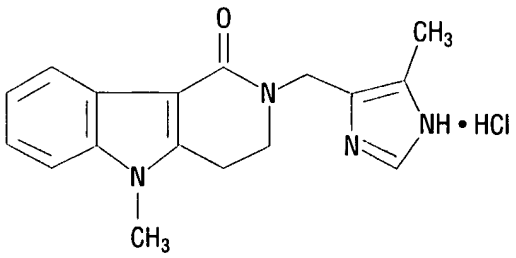
PRODUCT INFORMATION

LOTRONEX™

(alosetron hydrochloride)

Tablets

DESCRIPTION: The active ingredient in LOTRONEX Tablets is alosetron hydrochloride (HCl), a potent and selective antagonist of the serotonin 5-HT3 receptor type. Chemically, alosetron is designated as 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b] indol-1-one, monohydrochloride. Alosetron is achiral and has the empirical formula: $C_{17}H_{18}N_4O \cdot HCl$, representing a molecular weight of 330.8. Alosetron is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1M hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and <0.1 mg/mL in pH 8 phosphate buffer. The chemical structure of alosetron is:



LOTRONEX Tablets for oral administration contain 1.124 mg alosetron HCl equivalent to 1 mg of alosetron. Each tablet also contains the inactive ingredients, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

CLINICAL PHARMACOLOGY:

Pharmacodynamics: ***Mechanism of Action***: Alosetron is a potent and selective 5-HT3 receptor antagonist. 5-HT3 receptors are nonselective cation channels that are extensively distributed on enteric neurons in the human gastrointestinal tract, as well as other peripheral and central locations. Activation of these channels and the resulting neuronal depolarization affect the regulation of visceral pain, colonic transit and gastrointestinal secretions,

processes that relate to the pathophysiology of irritable bowel syndrome (IBS). 5-HT3 receptor antagonists such as alosetron inhibit activation of non-selective cation channels which results in the modulation of the enteric nervous system.

The cause of IBS is unknown. IBS is characterized by visceral hypersensitivity and hyperactivity of the gastrointestinal tract, which lead to abnormal sensations of pain and motor activity. Following distention of the rectum, IBS patients exhibit pain and discomfort at lower volumes than healthy volunteers. Following such distention, alosetron reduced pain and exaggerated motor responses, possibly due to blockade of $5HT_3$-receptors.

In healthy volunteers and IBS patients, alosetron (2 mg orally, twice daily for 8 days) increased colonic transit time without affecting orocecal transit time. In healthy volunteers, alosetron also increased basal jejunal water and sodium absorption after a single 4-mg dose. In IBS patients, multiple oral doses of alosetron (4 mg twice daily for 6.5 days) significantly increased colonic compliance.

Single oral doses of alosetron administered to healthy men produced a dose-dependant reduction in the flare response seen after intradermal injection of serotonin. Urinary 6-β-hydroxycortisol excretion decreased by 52% in elderly subjects after 27.5 days of alosetron 2 mg orally twice daily. This decrease was not statistically significant. In another study utilizing alosetron 1 mg orally twice daily for 4 days, there was a significant decrease in urinary 6-β-hydroxycortisol excretion. However, there was no change in the ratio of 6-β-hydroxycortisol to cortisol, indicating a possible decrease in cortisol production. The clinical significance of these findings is unknown.

Pharmacokinetics: The pharmacokinetics of alosetron have been studied after single oral doses ranging from 0.05 mg to 16 mg in healthy men. The pharmacokinetics of alosetron have also been evaluated in healthy women and men and in patients with IBS after repeated oral doses ranging from 1 mg twice daily to 8 mg twice daily.

Absorption: Alosetron is rapidly absorbed after oral administration with a mean absolute bioavailability of approximately 50 to 60% (approximate range 30 to >90%). After administration of radiolabeled alosetron, only 1% of the dose was recovered in the feces as

unchanged drug. Following oral administration of a 1 mg alosetron dose to young men, a peak plasma concentration of approximately 5 ng/mL occurs at 1 hour. In young women, the mean peak plasma concentration is approximately 9 ng/mL, with a similar time to peak.

***Food Effects*:** Alosetron absorption is decreased by approximately 25% by co-administration with food, with a mean delay in time to peak concentration of 15 minutes (see DOSAGE AND ADMINISTRATION).

Distribution: Alosetron demonstrates a volume of distribution of approximately 65 to 95 L. Plasma protein binding is 82% over a concentration range of 20 to 4000 ng/mL.

Metabolism and Elimination: Plasma concentrations of alosetron increase proportionately with increasing single oral doses up to 8 mg and more than proportionately at a single oral dose of 16 mg. Twice-daily oral dosing of alosetron does not result in accumulation. The terminal elimination half-life of alosetron is approximately 1.5 hours (plasma clearance is approximately 600 mL/min). Population pharmacokinetic analysis in IBS patients confirmed that alosetron clearance is minimally influenced by doses up to 8 mg.

Renal elimination of unchanged alosetron accounts for only 6% of the dose. Renal clearance is approximately 94 mL/min.

Alosetron is extensively metabolized in humans. The biological activity of these metabolites is unknown. A mass balance study was performed utilizing an orally administered dose of unlabeled and ^{14}C-labeled alosetron. This study indicates that on a molar basis, alosetron metabolites reach additive peak plasma concentrations 9-fold greater than alosetron and that the additive metabolite AUCs are 13 fold greater than alosetron's AUC. Plasma radioactivity declined with a half-life two-fold longer than that of alosetron, indicating the presence of circulating metabolites. Approximately 73% of the radiolabeled dose was recovered in urine with another 24% of the dose recovered in feces. Only 7% of the dose was recovered as unchanged drug. At least 13 metabolites have been detected in urine. The predominant product in urine was a 6-hydroxy metabolite (15% of the dose). This metabolite was secondarily metabolized to a glucuronide that was also present in urine (14% of the dose). Smaller amounts of the 6-hydroxy metabolite and the 6-O-glucuronide also appear to be present in feces. A bis-oxidized dicarbonyl accounted for 14% of the dose and its monocarbonyl precursor accounted for another 4% in urine and 6% in feces. No other

urinary metabolite accounted for more than 4% of the dose. Glucuronide or sulfate conjugates of unchanged alosetron were not detected in urine.

In studies of Japanese men, an N-desmethyl metabolite was found circulating in plasma in all subjects and accounted for up to 30% of the dose in one subject when alosetron was administered with food. The clinical significance of this finding is unknown.

Alosetron is metabolized by human microsomal cytochrome P450 (CYP), shown in vitro to involve enzymes 2C9 (30%), 3A4 (18%), and 1A2 (10%). Non-CYP mediated Phase I metabolic conversion also contributes to an extent of about 11% (see PRECAUTIONS: Drug Interactions).

Population Subgroups:

Age: In some studies in healthy men or women, plasma concentrations were elevated by approximately 40% in individuals 65 years and older compared to young adults. However, this effect was not consistently observed in men (see PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION: Geriatric Patients).

Gender: Plasma concentrations are 30% to 50% lower and less variable in men compared to women given the same oral dose. Population pharmacokinetic analysis in IBS patients confirmed that alosetron concentrations were influenced by gender (27% lower in men).

Reduced Hepatic Function: No pharmacokinetic data are available in this patient group (see PRECAUTIONS: Hepatic Insufficiency and DOSAGE AND ADMINISTRATION: Patients with Hepatic Impairment).

Reduced Renal Function: Renal impairment (creatinine clearance 4 to 56 mL/min) has no effect on the renal elimination of alosetron due to the minor contribution of this pathway to elimination. The effect of renal impairment on metabolite kinetics and the effect of end-stage renal disease have not been assessed (see DOSAGE AND ADMINISTRATION: Patients with Renal Impairment).

CLINICAL TRIALS: Two 12-week treatment, multi-center, double-blind, placebo-controlled, dose-ranging studies were conducted to determine the dosage of oral LOTRONEX for subsequent evaluation in efficacy studies.

In women, of the doses studied, 1 mg of LOTRONEX twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort, decreasing the proportion of days with urgency, decreasing stool frequency, and producing firmer stools. Efficacy in men,, as assessed by producing adequate relief of IBS pain and discomfort, was not demonstrated at any dose of LOTRONEX.

The efficacy and safety of 1 mg of oral LOTRONEX twice daily for 12 weeks was studied in two US multi-center, double-blind, placebo-controlled trials of identical design (Studies 1 and 2) in non-constipated women with IBS meeting the Rome Criteria (see Appendix) for at least 6 months. For enrollment into the studies, patients were required to meet entry pain and stool consistency criteria. An average pain score of at least mild pain, as collected during a two-week screening period, was required. Women with severe pain were excluded. An entry stool consistency requirement was also incorporated to target women whose predominant bowel symptom was diarrhea or in which diarrhea was a prominent feature in their alternating pattern. Women with a history of severe constipation were excluded. Men were not studied.

The primary efficacy measure in these studies was the woman's weekly assessment of adequate relief of IBS pain and discomfort. Key secondary measures included percentage of days with urgency and daily assessment of stool frequency and consistency. Study 1 enrolled 647 women (71% diarrhea-predominant, 28% alternating between diarrhea and constipation, and 1% constipation-predominant) while Study 2 enrolled 626 women (71% diarrhea-predominant, 27% alternating between diarrhea and constipation, and 2% constipation-predominant). At entry into the studies, most women reported mild to moderate pain intensity and stool consistency of formed to loose.

In both trials, LOTRONEX 1 mg administered twice daily was significantly more effective than placebo in providing relief of IBS pain and discomfort.

In both Study 1 and Study 2, the beneficial effect on IBS pain and discomfort was demonstrated only in women with diarrhea-predominant IBS. Data in Figures 1 and 2 are presented for this subgroup. In Study 1, significantly more women reported relief of their abdominal pain and discomfort within 1 week of starting alosetron therapy than those who received placebo (Figure 1) start. In Study 2, this treatment effect was observed within

4 weeks (Figure 2). Once attained, significant treatment effect persisted throughout the remainder of the treatment period. Upon discontinuing LOTRONEX, symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated women.

Figure 1: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 1

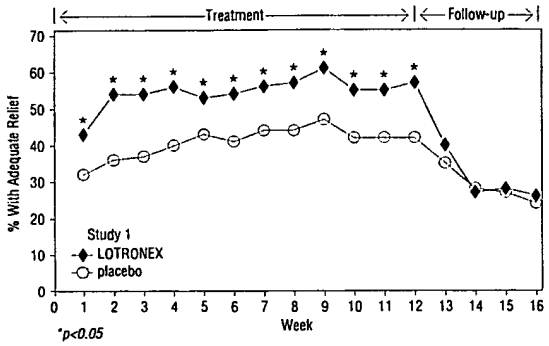
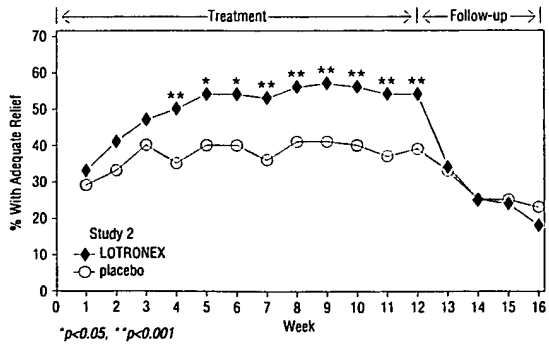


Figure 2: Percentage of Women (Diarrhea-Predominant) Reporting Relief of IBS Pain and Discomfort in Study 2



In each study, women who received LOTRONEX reported a significant decrease in the percentage of days with urgency as compared to those who received placebo. Treatment with LOTRONEX also resulted in firmer stools and a significant decrease in stool frequency.

Significant improvement of these symptoms occurred within the first week of treatment and persisted throughout the 12 weeks of therapy. Upon discontinuance of treatment these symptoms returned. Within one week after discontinuing therapy, there was no difference between placebo and alosetron-treated patients. The efficacy of LOTRONEX for treatment longer than 12 weeks has not been established.

INDICATIONS AND USAGE: LOTRONEX is indicated for the treatment of irritable bowel syndrome (IBS) in women whose predominant bowel symptom is diarrhea.

The safety and effectiveness of LOTRONEX in men have not been established.

CONTRAINDICATIONS: LOTRONEX is contraindicated in patients known to have hypersensitivity to any component of the product.

WARNINGS: Acute ischemic colitis was infrequently* reported in patients receiving LOTRONEX in 3-month clinical trials. The reported cases resolved over several days to weeks without sequelae or complications following supportive management. A causal association between treatment with LOTRONEX and acute colitis has not been established, nor have risk factors been identified. LOTRONEX should be discontinued in patients experiencing rectal bleeding and a sudden worsening of abdominal pain. These patients should be promptly evaluated and appropriate diagnostic testing considered

.

Constipation is a frequent and dose-related side effect of treatment with LOTRONEX. LOTRONEX should not be used in IBS patients who are currently constipated or whose predominant bowel symptom is constipation. In clinical studies, 25 to 30% of patients receiving alosetron experienced constipation. For the majority of these patients, constipation was mild to moderate in intensity and self-limited; however, approximately 9% of patients studied required interruption of treatment for a few days and approximately 10% could not tolerate twice daily dosing on a continuous basis and discontinued therapy. Patients

experiencing constipation who completed the 12-week treatment period had similar relief of abdominal pain as patients not experiencing constipation who completed the study. Management of constipation with usual care including laxatives, fiber, or with a brief interruption of therapy may be considered. (See DOSAGE AND ADMINISTRATION)

*Infrequent is defined as occurring in 1/100 to 1/1000 patients.

PRECAUTIONS:

Information for Patients: See the tear-off leaflet at the end of the labeling for Information for the Patient.

Drug Interactions: In vitro human liver microsome studies and an in vivo metabolic probe study demonstrated that alosetron did not inhibit CYP enzymes 2D6, 3A4, 2C9, or 2C19. In vitro, at total drug concentrations 27-fold higher than peak plasma concentrations observed with the 1-mg dosage, alosetron inhibited CYP enzymes 1A2 (60%) and 2E1 (50%). In an in vivo metabolic probe study, alosetron did not inhibit CYP2E1 but did produce 30% inhibition of both CYP1A2 and N-acetyltransferase. Although not studied with alosetron, inhibition of N-acetyltransferase may have clinically relevant consequences for drugs such as isoniazid, procainamide, and hydralazine. The effect on CYP1A2 was explored further in a clinical interaction study with theophylline and no effect on metabolism was observed. Another study showed that alosetron had no clinically significant effect on plasma concentrations of the oral contraceptive agents ethinyl estradiol and levonorgestrel (CYP3A4 substrates). A clinical interaction study was also conducted with alosetron and the CYP3A4 substrate cisapride. No significant effects on cisapride metabolism or QT interval were noted. The effect of alosetron on monoamine oxidases and on intestinal first pass secondary to high intraluminal concentrations have not been examined. Based on the above data from in vitro and in vivo studies, it is unlikely that alosetron will inhibit the hepatic metabolic clearance of drugs metabolized by the major CYP enzyme 3A4, as well as the CYP enzymes 2D6, 2C9, 2C19, 2E1, or 1A2.

Alosetron does not appear to induce the major cytochrome P450 (CYP) drug metabolizing enzyme 3A. Alosetron also does not appear to induce CYP enzymes 2E1 or 2C19. It is not known whether alosetron might induce other enzymes.

Because alosetron is metabolized by a variety of hepatic CYP drug-metabolizing enzymes, inducers or inhibitors of these enzymes may change the clearance of alosetron. The effect of induction or inhibition of individual pathways on metabolite kinetics and pharmacodynamic consequences has not been examined.

Hepatic Insufficiency: Due to the extensive hepatic metabolism and first pass metabolism of alosetron and metabolites, increased exposure to alosetron is likely to occur in patients with hepatic insufficiency.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In 2-year oral studies, alosetron was not carcinogenic in mice at doses up to 30 mg/kg/day or in rats at doses up to 40 mg/kg/day. These doses are, respectively, about 60 to 160 times the recommended human dose of alosetron of 2 mg/day (1 mg twice daily)based on body surface area. Alosetron was not genotoxic in the Ames tests, the mouse lymphoma cell (L5178Y/TK$^{\pm}$) forward gene mutation test, the human lymphocyte chromosome aberration test, the ex vivo rat hepatocyte unscheduled DNA synthesis (UDS) test, or the in vivo rat micronucleus test for mutagenicity. Alosetron at oral doses up to 40 mg/kg/day (about 160 times the recommended daily human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male or female rats.

Pregnancy: Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats at doses up to 40 mg/kg/day (about 160 times the recommended human dose based on body surface area) and rabbits at oral doses up to 30 mg/kg/day (about 240 times the recommended daily human dose based on body surface area). These studies have revealed no evidence of impaired fertility or harm to the fetus due to alosetron. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, LOTRONEX should be used during pregnancy only if clearly needed.

Nursing Mothers: Alosetron and/or metabolites of alosetron are excreted in the breast milk of lactating rats. It is not known whether alosetron is excreted in human milk. Because many

drugs are excreted in human milk, caution should be exercised when LOTRONEX is administered to a nursing woman.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: Of all patients who received at least one dose of alosetron in premarketing studies, 211 were 65 years of age and over and 39 were 75 years of age and over. The safety profile of LOTRONEX was similar in older and younger patients.

In two placebo-controlled IBS safety and efficacy trials (Studies 1 and 2), 60 patients 65 years of age and over and 14 patients 75 years of age and over received 1-mg oral doses of LOTRONEX twice daily for up to 12 weeks. In both studies, subgroup analyses showed no evidence of differential treatment effects across the age categories assessed. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out (see CLINICAL PHARMACOLOGY: Population Subgroups: Age).

ADVERSE REACTIONS: In two large, placebo-controlled clinical trials conducted in the US (Studies 1 and 2), women (18 years of age and older) were treated with 1 mg of LOTRONEX twice-daily for up to 12 weeks. The adverse events in Table 1 were reported in 1% or more of patients who received LOTRONEX and occurred more frequently on LOTRONEX than on placebo: a statistically significant difference was observed for constipation in patients treated with LOTRONEX compared to placebo ($p<0.0001$).

Table 1: Adverse Events Reported in ≥1% of Female Patients and More Frequently on LOTRONEX 1 mg B.I.D. than Placebo (Studies 1 and 2)

Body System Adverse Event	LOTRONEX (N = 632)	Placebo (N = 637)
Cardiovascular		
Hypertension	2%	<1%
Ear, Nose, and Throat		
Allergic rhinitis	2%	<1%
Throat and tonsil discomfort and pain	1%	<1%
Bacterial ear, nose, and throat infections	1%	<1%
Gastrointestinal		
Constipation	28%	5%
Nausea	7%	6%
Gastrointestinal discomfort and pain	5%	4%
Abdominal discomfort and pain	5%	3%
Gastrointestinal gaseous symptoms	3%	2%
Viral gastrointestinal infections	3%	2%
Dyspeptic symptoms	3%	1%
Abdominal distention	2%	<1%
Hemorrhoids	2%	<1%
Neurology		
Sleep disorders	3%	2%
Psychiatry		
Depressive disorders	2%	1%

Gastrointestinal: The most frequent adverse event reported by patients treated with LOTRONEX was constipation (see WARNINGS). In clinical studies, constipation was reported in 25 to 30% of patients treated with LOTRONEX 1 mg twice daily for up to 12 weeks (n = 702). This effect was statistically significant compared to placebo ($p<0.0001$). Ten percent (10%) of patients treated with LOTRONEX withdrew from the studies due to constipation. Of the patients reporting constipation, 75% reported a single episode with the mean time to constipation onset of about 3 weeks. Occurrences of constipation were generally mild to moderate in intensity and transient in nature. Most constipation events resolved spontaneously with continued treatment. In studies 1 and 2, 9% of patients treated with LOTRONEX reported constipation and 4 consecutive days with no bowel movement; by protocol, therapy was withheld for 1 to 4 days. Following interruption of treatment, 88% of the affected patients resumed bowel movements within the 4-day period and were able to re-initiate treatment with LOTRONEX.

Hepatic: A similar incidence in elevation of ALT (>3-fold) was seen in patients receiving LOTRONEX or placebo (0.5% vs 0.4%) in studies of 12 weeks' and 12 months' duration. A single case of hepatitis (elevated ALT, AST, alkaline phosphatase, and bilirubin) without jaundice was reported in a 12-week study. A causal association with LOTRONEX has not been established.

Long-Term Safety: The pattern and frequency of adverse events in a long-term, placebo-controlled safety study in which women with IBS (n = 473) were treated with LOTRONEX 1 mg twice daily for up to 12 months were essentially the same as observed in 12-week safety and effectiveness trials. There were no reports of acute colitis in these alosetron-treated women.

Other Events Observed During the Premarketing Evaluation of LOTRONEX: During its premarketing assessment, multiple and single doses of LOTRONEX were administered resulting in 2574 patient exposures in 46 completed clinical studies. The conditions, dosages, and duration of exposure to LOTRONEX varied between trials, and the studies included healthy male and female volunteers as well as male and female patients with IBS.

In the listing that follows, reported adverse events were classified using a standardized coding dictionary. Only those events that an investigator believed were possibly related to

alosetron, occurred in at least 2 patients, and occurred at a greater frequency during treatment with LOTRONEX than during placebo administration are presented. Serious adverse events occurring in at least one patient for which an investigator believed there was reasonable possibility that the event was related to alosetron treatment and which occurred at a greater frequency in LOTRONEX than placebo-treated patients are also presented.

In the following listing, events are categorized by body system. Within each body system, events are presented in descending order of frequency. The following definitions are used: *Infrequent* adverse events are those occurring on one or more occasion in 1/100 to 1/1000 patients; *Rare* adverse events are those occurring on one or more occasion in fewer than 1/1000 patients.

Although the events reported occurred during treatment with LOTRONEX, they were not necessarily caused by it.

Cardiovascular - Infrequent: Arrhythmias.

***Drug Interaction, Overdose and Trauma - Rare*:** Contusions and hematomas.

Ear Nose, and Throat - Infrequent*:** Nasal signs and symptoms. ***Rare: Ear signs and symptoms.

Eyes - Rare: Photophobia.

Gastrointestinal –Infrequent: Ischemic colitis. ***Rare:*** proctitis.

***Hepatobiliary Tract and Pancreas - Infrequent*:** Abnormal bilirubin levels.

Lower Respiratory - Infrequent*:** Breathing disorders. ***Rare: Cough.

***Neurological - Rare*:** Sedation and abnormal dreams.

Non-site Specific - Rare: Allergies, allergic reactions, unusual odors and taste.

***Psychiatry - Infrequent*:** Anxiety.

Reproduction - Infrequent*:** Menstrual disorders. ***Rare: Sexual function disorders.

Skin - Rare: Acne and folliculitis.

***Urology - Rare*:** Urinary infections, polyuria, and diuresis.

DRUG ABUSE AND DEPENDENCE: LOTRONEX has no known potential for abuse or dependence.

OVERDOSAGE: There is no specific antidote for overdose of LOTRONEX. Patients should be managed with appropriate supportive therapy. Individual oral doses as large as 16 mg have been administered in clinical studies without significant adverse events. This dose is 8 times higher than the recommended total daily dose. Inhibition of the metabolic elimination and reduced first pass of other drugs might occur with overdoses of alosetron (see PRECAUTIONS: Drug Interactions). Single oral doses of LOTRONEX at 15 mg/kg in female mice and 60 mg/kg in female rats (30 and 240 times, respectively, the recommended human dose based on body surface area) were lethal. Symptoms of acute toxicity were labored respiration, subdued behavior, ataxia, tremors, and convulsions.

DOSAGE AND ADMINISTRATION:

Usual Dose in Adults: The recommended adult dosage of LOTRONEX is 1 mg taken orally twice daily with or without food. Individual patients who experience constipation may need to interrupt treatment (see WARNINGS and ADVERSE REACTIONS: Gastrointestinal).

Pediatric Patients: No studies have been conducted in patients less than 18 years of age (see PRECAUTIONS: Pediatric Use).

Geriatric Patients: No dosage adjustment is recommended for elderly patients (65 years of age and older) (see CLINICAL PHARMACOLOGY: Population Subgroups: Age and PRECAUTIONS: Geriatric Use).

Patients with Renal Impairment: No dosage adjustment is recommended for patients with renal impairment (creatinine clearance 4 to 56 mL/min) (see CLINICAL PHARMACOLOGY: Reduced Renal Function).

Patients with Hepatic Impairment: No studies have been conducted in patients with hepatic impairment (see PRECAUTIONS: Hepatic Insufficiency and CLINICAL PHARMACOLOGY: Population Subgroups: Reduced Hepatic Function).

HOW SUPPLIED: LOTRONEX Tablets, 1 mg (1.124 mg alosetron HCl equivalent to 1 mg alosetron), are blue, oval, film-coated tablets engraved with GX CT1 on one face in bottles

of 60 tablets (NDC 0173-0690-00) and 120 tablets (NDC 0173-0690-03) with child-resistant closures and Unit Dose Pack of 60 (NDC 0173-0690-04).

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

APPENDIX

Diagnostic Criteria: Irritable Bowel Syndrome (IBS)*
At least three months continuous or recurrent symptoms of: **1. abdominal pain or discomfort which is:** **(a) relieved with defecation,** **(b) and/or associated with a change in frequency of stool,** **(c) and/or associated with a change in consistency of stool;** **and** **1. two or more of the following, at least a quarter of occasions or days;** **(a) altered stool frequency,** **(b) altered stool form (lumpy/hard or loose/watery stool),** **(c) altered stool passage (straining, urgency, or feeling of incomplete evacuation),** **(d) passage of mucus,** **(e) bloating or feeling of abdominal distention**

*Thompson WG, Creed F. Drossman DA, et al. Functional bowel disease and functional abdominal pain, Gastroenterol Int 1992; 5: 75-91.

GlaxoWellcome

Glaxo Wellcome Inc.

Research Triangle Park, NC 27709

US Patent No. 5,360,800

Date of Issue: February 2000 RL-XXX

PHARMACIST--DETACH HERE AND GIVE LEAFLET TO PATIENT.

Information for the Patient

LOTRONEX™(alosetron hydrochloride) Tablets

Read this information carefully before you start taking LOTRONEX (pronounced LOW-trah-nex) Tablets. Read the information included with LOTRONEX each time you refill your prescription, in case something has changed. This information does not take the place of discussions with your doctor.

What is LOTRONEX?

LOTRONEX is a prescription medicine used to treat irritable bowel syndrome (IBS) in women who have diarrhea as their main symptom. Lotronex has not been shown to work in men with IBS. IBS has been called by many names including irritable colon, and spastic colon. IBS is a medical condition causing cramping abdominal pain, abdominal discomfort, urgency (a sudden need to have a bowel movement), and irregular bowel habits such as diarrhea or constipation.

It is not clear why some people develop IBS. It may be caused by your body's overreaction to a body chemical called serotonin. This overreaction may cause your intestinal system to be overactive. LOTRONEX works by blocking the action of serotonin on the intestinal system. This reduces the cramping abdominal pain, abdominal discomfort, urgency, and diarrhea caused by IBS.

LOTRONEX may not work for every patient who takes it. For women who are helped by LOTRONEX, the medicine works faster in some and slower in others. Some women taking LOTRONEX will have relief from their IBS pain and discomfort within the first week of

use. Other women have relief of abdominal pain and discomfort within four weeks of starting LOTRONEX. Within one week, urgency and diarrhea occur less often for some patients. When you stop taking LOTRONEX, IBS symptoms will likely return within one week.

A. Who should not take LOTRONEX?

You should not start taking LOTRONEX when you are constipated or constipated most of the time.

Do not take LOTRONEX if you are allergic to LOTRONEX or any of its ingredients. The active ingredient in LOTRONEX is alosetron hydrochloride. The inactive ingredients are listed at the end of this leaflet.

Lotronex may not be right for you. Tell your doctor if you are:

- constipated most of the time.
- pregnant or plan to become pregnant.
- breast feeding.
- taking or planning to take any other medicines, including those you can get without a prescription.

B. How should LOTRONEX be taken?

Take LOTRONEX exactly as your doctor prescribes it. You can take Lotronex with or without food. If you miss a dose of LOTRONEX, do not double the next dose. Instead, simply go to the next regularly scheduled dosing time and take your normal prescribed dose of LOTRONEX

What are the possible side effects of LOTRONEX?

If you have a sudden worsening of abdominal pain or if you see blood in your stool (bowel movement), call your doctor right away. These symptoms may be a sign of a serious medical condition.

Constipation is a common side effect of treatment with LOTRONEX. If you become constipated while taking LOTRONEX, call your doctor. Your doctor may tell you to stop taking LOTRONEX or suggest other ways to manage your constipation.

This description of side effects is not complete. Your doctor or pharmacist can give you a more complete list of side effects with LOTRONEX. Talk to your doctor right away about any side effects you have.

Medicines are sometimes prescribed for purposes not listed in patient information leaflets. Do not use Lotronex for a condition for which it was not prescribed. Do not share Lotronex with other people. As with any medicine, LOTRONEX may be harmful without appropriate medical supervision.

If you have questions about Lotronex, ask your doctor or pharmacist. They can show you detailed information about Lotronex that was written for health professionals.

Inactive Ingredients: Lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and pregelatinized starch. The blue film-coat contains hydroxypropyl methylcellulose, titanium dioxide, triacetin, and indigo carmine.

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EXHIBIT 5

United States Patent No. 5,360,800

Express Mail Label No. EM484297842US

US005360800A

United States Patent [19]

Coates et al.

[11] Patent Number: 5,360,800

[45] Date of Patent: * Nov. 1, 1994

[54] **TETRAHYDRO-1H-PYRIDO[4,3-B]INDOL-1-ONE DERIVATIVES**

[75] Inventors: Ian H. Coates, Hertford; Peter C. North; Alexander W. Oxford, both of Royston, all of England

[73] Assignee: Glaxo Group Limited, London, England

[*] Notice: The portion of the term of this patent subsequent to Feb. 2, 2010 has been disclaimed.

[21] Appl. No.: 741,570

[22] Filed: Aug. 7, 1991

Related U.S. Application Data

[63] Continuation of Ser. No. 602,771, Oct. 24, 1990, abandoned, which is a continuation of Ser. No. 239,626, Sep. 2, 1988, abandoned.

[30] Foreign Application Priority Data

Sep. 3, 1987 [GB] United Kingdom 8720695
Aug. 15, 1988 [GB] United Kingdom 8819382

[51] Int. Cl.[5] C07D 401/06; C07D 471/04; A61K 31/44; A61K 31/55

[52] U.S. Cl. 514/215; 514/292; 540/524; 546/86; 546/87

[58] Field of Search 546/85, 86, 87; 540/524; 514/292, 215

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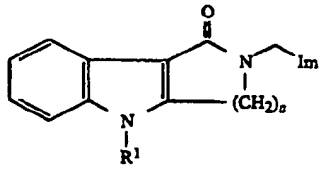
Primary Examiner—Alan L. Rotman
Attorney, Agent, or Firm—Bacon & Thomas

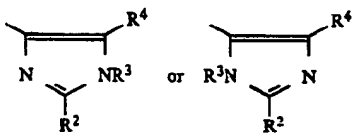
[57] ABSTRACT

The invention relates to tricyclic lactams of the general formula (I)



(I)

wherein Im represents an imidazolyl group of the formula:



and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl, phenyl C_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl or phenoxymethyl,

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenyl C_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6}alkhyl group;

n represents 2 or 3; and physiologically acceptable salts and solvates thereof.

The compounds are potent and selective antagonists of the effect of 5-HT at 5-HT_3 receptors and are useful, for example, in the treatment of psychotic disorders, anxiety, and nausea and vomiting.

35 Claims, No Drawings

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TETRAHYDRO-1H-PYRIDO[4,3-B]INDOL-1-ONE DERIVATIVES

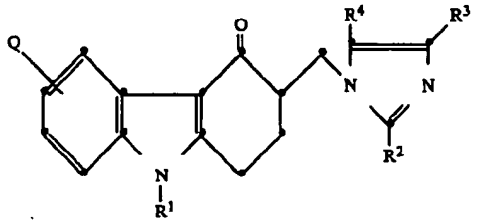
This application is a continuation of application Ser. No. 07/602,771, filed Oct. 24, 1990, abandoned which is a continuation of application Ser. No. 07/239,626, filed Sep. 2, 1988, now abandoned.

This invention relates to lactam derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their medical use.

In particular the invention relates to compounds which are potent and selective antagonists of 5-hydroxytryptamine (5-HT) at 5-HT receptors of the type located on terminals of primary afferent nerves. Receptors of this type are now designated as 5-HT3receptors and are also present in the central nervous system. 5-HT occurs widely in the neuronal pathways in the central nervous system and disturbance of these 5-HT containing pathways is known to alter behavioural syndromes such as mood, psychomotor activity, appetite and memory.

Compounds having antagonist activity at 5-HT_3 receptors have been described previously.

Thus for example published UK Patent Specification No. 2153821A and published European Patent Specifications Nos. 191562, 219193 and 210840 disclose 3-imidazolylmethyltetrahydrocarbazolones which may be represented by the general formula:



wherein R^1 represents a hydrogen atom or a group selected from C_{1-10}alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4}alkyl, phenyl or phenylC_{1-3}alkyl, and in the case where Q represents a hydrogen atom, R^1 may also represent $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ (wherein R^5 and R^6, which may be the same or different, each represents a hydrogen atom, a C_{1-6} alkyl or C_{3-7}cycloalkyl group, or a phenyl or phenylC_{1-4}alkyl group, in which the phenyl group is optionally substituted by one or more C_{1-4} alkyl, C_{1-4}alkoxy or hydroxy groups or halogen atoms, with the proviso that R^5 does not represent a hydrogen atom when R^1 represents a group $-CO_2R^5$ or $-SO_2R^5$);

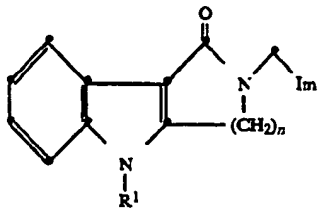
one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6} alkyl, C_{3-7} cycloalkyl, C_{2-6} alkenyl, or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

Q represents a hydrogen atom or a halogen atom or a hydroxy, C_{1-4}alkoxy, phenylC_{1-3}alkoxy or C_{1-6} alkyl group or a group $-NR^7R^8$ or $-CONR^7R^8$ (wherein R^7 and R^8, which may be the same or different, each represents a hydrogen atom or a C_{1-4} alkyl or C_{3-4} alkenyl group, or together with the nitrogen atom to which they are attached form a saturated 5 to 7 membered ring);

and physiologically acceptable salts and solvates thereof.

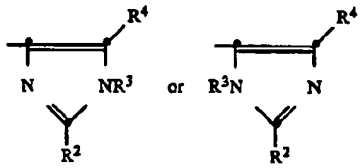
We have now found a noval group of compounds which differ in structure from those described previously, and which are potent antagonists of the effect of 5-HT at 5-HT_3 receptors.

The present invention provides a tricyclic lactam of the general formula (I):



(I)

wherein Im represents an imidazolyl groups of the formula:



and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl, phenoxymethyl, $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ (wherein R^5 and R^6, which may be the same or different, each represents a hydrogen atom, a C_{1-6} alkyl or C_{3-7} cycloalkyl group, or a phenyl or phenylC_{1-4}alkyl group, in which the phenyl group is optionally substituted by one or more C_{1-4} alkyl, C_{1-4} alkoxy or hydroxy groups or halogen atoms, with the proviso that R^5 does not represent a hydrogen atom when R^1 represents a group $-CO_2R^5$ or $-SO_2R^5$);

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6} alkyl group;

n represents 2 or 3; and physiologically acceptable salts and solvates thereof.

According to one aspect, the invention provides compounds of formula (I) wherein R^1 represents a hydrogen atom or a group selected from C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, phenyl or phenylC_{1-3} alkyl (n and Im being as defined in formula (I)).

Suitable physiologically acceptable salts of the compounds of general formula (I) include acid addition salts formed with organic or inorganic acids for example, hydrochlorides, hydrobromides, sulphates, alkyl- or arylsulphonates (e.g. methanesulphonates or p-toluenesulphonate), phosphates, acetates, citrates, succinates, tartrates, fumarates and maleates. The solvents may, for example, be hydrates.

All optical isomers of compounds of general formula (I) and their mixtures including the racemic mixtures thereof, and all the geometric isomers of compounds of formula (I), are embraced by the invention.

Referring to the general formula (I), an alkyl group may be a straight chain or branched chain alkyl group, for example, methyl, ethyl, n-propyl, prop-2-yl, n-butyl, but-2-yl, 2-methylprop-2-yl, n-pentyl, pent-3-yl or n-hexyl, A C_{3-6} alkenyl group may be, for example, a propenyl or butenyl group. When R^1 represents a C_{3-6}alkenyl or C_{3-10}alkynyl group, or R^3 represents a C_{3-6}alkenyl group, or R^7 or R^8 represents a C_{3-4}alkenyl group, the double or triple bond may not be adjacent to the nitrogen atom. A phenylC_{1-3}alkyl group may be, for example, a benzyl, phenethyl or 3-phenylpropyl group. A C_{3-7}cycloalkyl group may be, for example, a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl group.

A preferred class of compounds of formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-6} alkyl (e.g. methyl, ethyl, n-propyl, prop-2-yl), C_{3-4} alkenyl (e.g. prop-2-enyl), C_{3-4} alkynyl (e.g. prop-2-ynyl), C_{5-6}cycloalkyl (e.g. cyclopentyl), C_{5-6}cycloalkylmethyl (e.g. cyclopentylmethyl), phenylC_{1-2} alkyl (e.g. benzyl), phenylmethoxymethyl, N,N-diC_{1-3}alkylcarboxamido (e.g. N,N-dimethylcarboxamido) or C_{1-3}alkylsulphonyl (e.g. methylsulphonyl) group. More preferably R^1 represents a C_{1-4} alkyl (e.g. methyl or n-propyl), C_{3-4}alkynyl (e.g. prop-2-ynyl), C_{5-6}cycloalkyl (e.g. cyclopentyl), C_{5-6}cycloalkylmethyl (e.g. cyclopentylmethyl), phenylC_{1-2} alkyl (e.g. benzyl), phenylmethoxymethyl, or N,N-diC_{1-3}alkylcarboxamido (e.g. N,N-dimethylcarboxamido) group.

Another preferred class of compounds of formula (I) is that wherein R^2 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl) group, more preferably a hydrogen atom.

Another preferred class of compounds of formula (I) is that wherein R^3 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl) group, more preferably a hydrogen atom.

A further preferred class of compounds of formula (I) is that wherein R^4 represents a hydrogen atom or a C_{1-3} alkyl (e.g. methyl or n-propyl) group. Most preferably r^4 represents a methyl group.

When R^2 and R^3 represent hydrogen atoms, R^4 is preferably C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{3-6} alkenyl or phenylC_{1-3}alkyl, more particularly C_{1-6} alkyl.

A further preferred class of compounds of formula (I) is that wherein n represents 2.

A preferred group of compounds of formula (I) is that wherein R^1 represents a hydrogen atom or a C_{1-4} alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloalkyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2} alkyl, phenylmethoxymethyl, N,N-diC_{1-3}alkylcarboxamido or C_{1-3}alkylsulphonyl group; R^2 represents a hydrogen atom; and R^3 and r^4 each represent a hydrogen atom or a C_{1-3} alkyl group.

A particularly preferred group of compounds of formula (I) is that wherein R^1 represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, benzyl or N,N-dimethylcarboxamido group; R^2 and R^3 each represent a hydrogen atom; and R^4 represents a methyl group.

Within the above preferred and particularly preferred groups of compounds, an especially important group of compounds is that in which n represents 2.

Preferred compounds according to the invention are:

2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;

2,3,4,5-tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;

5-cyclopentyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4yl)-methyl]-1H-pyrido[4,3-b]indol-1-one;

2,3,4,5-tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;

5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl) methyl]-1H-pyrido[4,3-b]indol-1-one;

3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one;

2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-methyl-1H-imidazol-4yl)-methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide;

2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one;

and their physiologically acceptable salts and solvates.

The potent and selective antagonism of 5HT at 5-HT_3 receptors by compounds of the invention has been demonstrated by their ability to inhibit 3-(5-methyl-1H-imidazol-4yl)-1-[1-(methyl-t_3)-1H-indol-3yl]-1-propanone binding in rat entorhinal cortex homogenates (following the general procedure described by G. Kilpatrick et al. in *Nature*, 1987, 330, 746), and/or by their ability to inhibit the 5-HT-induced depolarisation of the rate isolated vagus nerve preparation.

In addition to their activity as potent and selective antagonists of 5-HT at 5-HT_3 receptors, certain compounds according to the invention have the advantage of an extended duration of action.

a particularly preferred compound on account of both its potency and duration of action is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one and its physiologically acceptable salts and solvates. Preferred salts of this compound are the hydrochloride and maleate.

Compounds of formula (I), which antagonise the effect of 5-HT at 5-HT_3 receptors, are useful in the treatment of conditions such as psychotic disorders (e.g. schizophrenia and mania); anxiety; and nausea and vomiting, particularly that associated with cancer chemotherapy and radiotherapy. Compounds of formula (I) are also useful in the treatment of gastric stasis; symptoms of gastrointestinal dysfunction such as occur with dyspepsia, peptic ulcer, reflux oesophagitis, flatulence and irritable bowel syndrome; migraine; and pain. Compounds of formula (I) may also be used in the treatment of dependency on drugs and substances of abuse, depression, and dementia and other cognitive disorders.

According to another aspect, the invention provides a method of treatment of a human or animal subject suffering from a psychotic disorder such as schizophrenia or mania; or from anxiety; nausea or vomiting; gastric stasis; symptoms of gastrointestinal dysfunction such as dyspepsia, reflux oesophagitis, peptic ulcer, flatulence and irritable bowel syndrome; migraine; or pain, which comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

Accordingly, the invention also provides a pharmaceutical composition which comprises at least one com-

pound selected from compounds of the general formula (I), and their physiologically acceptable salts and solvates (e.g. hydrates), for use in human or veterinary medicine, and formulated for administration by any convenient route.

Such compositions may be formulated in conventional manner using one or more physiologically acceptable carriers and/or excipients.

Thus the compounds according to the invention may be formulated for oral, buccal, parenteral or rectal administration or in a form suitable for administration by inhalation or insufflation (either through the mouth or nose).

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxylpropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium starch glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparation for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents (e.g. sorbitol syrup, cellulose derivatives or hydrogenated edible fats); emulsifying agents (e.g. lecithin or acacia); non-aqueous vehicles (e.g. almond oil, oily esters, ethyl alcohol or fractionated vegetable oils); and preservatives (e.g. methyl or propyl-p-hydroxybenzoates or sorbic acid). The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds of the invention may be formulated for parenteral administration by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form e.g. in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterily pyrogen-free water, before use.

The compounds of the invention may also be formulated in rectal compositions such as suppositories or retention enemas, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

In addition to the formulations described previously, the compounds of the invention may also be formulated as depot preparations. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example as a sparingly soluble salt.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs or a nebuliser, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

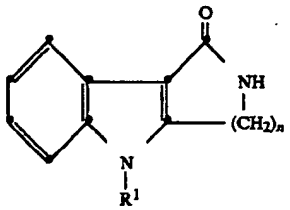
For intra nasal administration, the compounds according to the invention may be formulated as solutions for administration via a suitable metered or unit dose device or alternatively as a powder mix with a suitable carrier for administration using a suitable delivery device.

The compounds of formula (I) may also be administered in combination with other therapeutic agents. Thus, for example, in the treatment of gastric stasis, symptoms of gastrointestinal dysfunction and nausea and vomiting, the compounds of formula (I) may be administered in combination with antisecretory agents such as histamine H_2-receptor antagonists (e.g. ranitidine, sufotidine, 1-methyl-5-[[3-[3-(1-piperidinylmethyl)phenoxy]propyl]amino]-1H-1,2,4-triazole-3-methanol, cimetidine, famotidine, nizatidine or roxatidine) or H+K+ATPase inhibitors (e.g. omeprazole).

A proposed dose of the compounds of the invention for administration to man (of approximately 70 kg body weight) is 0.001 to 100 mg, preferably 0.01 to 50 mg, more preferably 0.1 to 20 mg of the active ingredient per unit dose expressed as the weight of free base, which could be administered, for example, 1 to 4 times per day. It will be appreciated that it may be necessary to make routine variations to the dosage, depending on the age and condition of the patient. The dosage will also depend on the route of administration.

Compounds of general formula (I) and physiologically acceptable salts or solvates thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R^1, n, and Im are as defined for compounds of general formula (I) unless otherwise stated.

According to a first general process (A), a compound of general formula (I) may be prepared by alkylating a compound of formula (II):



(II)

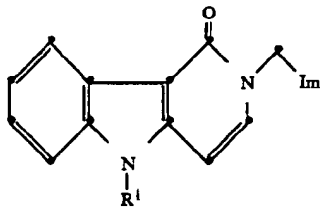
with a compound of formula (III):

LCH_2-Im (III)

or a protected derivative thereof, wherein L represents a leaving atom or group, such as a halogen atom (e.g. chlorine, bromine or iodine), or an acyloxy group (e.g. trifluoroacetyloxy or acetoxy), or a sulphonyloxy group (e.g. trifluoromethanesulphonyloxy, p-toluenesulphonyloxy or methanesulphonyloxy), followed wherein necessary by removal of any protecting groups. L is preferably a halogen atom (e.g. a chlorine atom).

The reaction may be carried out in an inert solvent such as an ether (e.g. dimethoxyethane, diglyme or tetrahydrofuran), a substituted amide (e.g. dimethylformamide or N-methylpyrrolidone), an aromatic hydrocarbon (e.g. toluene), a ketone (e.g. acetone), or dimethyl sulphoxide, at a temperature between ambient and 100° C., in the presence of a base. Suitable bases include alkali metal hydrides (e.g. sodium hydride), alkali metal carbonates (e.g. sodium carbonate), alkali metal amides (e.g. sodium amide), alkali metal alkoxides (e.g. potassium t-butoxide) or alkali metal hydroxides (e.g. sodium or potassium hydroxide).

According to another general process (B), a compound of general formula (I) wherein n represents 2, may be prepared by hydrogenation of a compound of formula (IV):

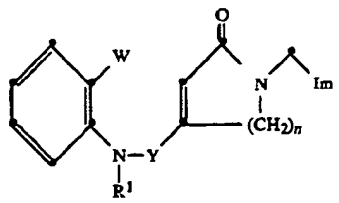


(IV)

or a protected derivative thereof, followed where necessary by removal of any protecting groups.

Hydrogenation according to general process (B) may be effected using conventional procedures, for example using hydrogen in the presence of a noble metal catalyst (e.g. palladium, Raney nickel, platinum or rhodium). The catalyst may be supported on, for example, charcoal or alumina, or alternatively a homogeneous catalyst such as tris(triphenylphosphine)rhodium chloride may be used. The hydrogenation will generally be effected in a solvent such as an alcohol (e.g. methanol or ethanol), an ether (e.g. dioxan), or an ester (e.g. ethyl acetate), or in a mixture of an alcohol and either a hydrocarbon (e.g. toluene) or a halogenated hydrocarbon (e.g. dichloromethan), at a temperature in the range −20° to +100° C., and at a pressure of from 1 to 10 atmospheres.

According to another general process (C), a compound of general formula (I) may be prepared by cyclising a compound of formula (V):



(V)

wherein W represents a hydrogen atom and Y represents the group NH, or W represent a halogen atom and Y represents a bond, or a salt or protected derivative thereof, followed where necessary by removal of any protecting groups.

According to one embodiment (a) of process (C), the reaction is effected with a compound of formula (V) wherein W represents a hydrogen atom and Y represents the group NH, and the cyclisation may be carried out in aqueous or non-aqueous media, in the presence of an acid catalyst.

It will be appreciated that these compounds of formula (V) may exist in the corresponding enol hydrazone tautomeric form.

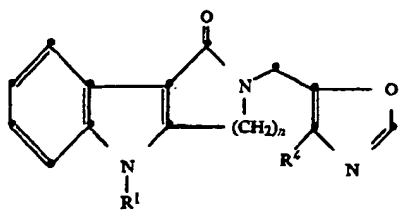
When an aqueous medium is employed this may be water or a mixture of water and a organic solvent such as an alcohol (e.g. methanol, ethanol or isopropanol) or an ether (e.g. dioxan or tetrahydrofuran). The acid catalyst may be, for example, an inorganic acid such as concentrated hydrochloric or sulphuric acid. In some cases the acid catalyst may also act as the reaction solvent. In an anhydrous reaction medium, which may comprise one or more alcohols or ethers (e.g. as described above), carboxylic acids (e.g. acetic acid) or esters (e.g. ethyl acetate), the acid catalyst may alternatively by a Lewis acid such as boron trifluoride, zinc chloride or magnesium chloride. The cyclisation reaction may conveniently be carried out at temperatures of from 20° to 200° C., preferably 20° to 125° C.

Alternatively the cyclisation according to embodiment (a) of process (C) may be carried out in the presence of polyphosphate ester in a reaction medium which may comprise one or more organic solvents, preferably halogenated hydrocarbons such as chloroform, dichloromethane, dichloroethane, dichlorodifluoromethane, or mixtures thereof. Polyphosphate ester is a mixture of esters which may be prepared from phosphorus pentoxide, diethyl ether and chloroform according to the method described in 'Reagents for Organic Synthesis', (Fieser and Fieser, John Wiley and Sons, 1967).

According to another embodiment (b) of process (C), the reaction is effected with a compound of formula (V) wherein W represents a halogen atom, for example, a chlorine atom or, more preferably, a bromine or iodine atom, Y represents a bond, and the cyclisation is effected photochemically.

The reaction may conveniently be effected by irradiating with a mercury lamp, preferably a medium or high pressure mercury lamp. Suitable solvents include nitriles (e.g. acetonitrile), chlorinated hydrocarbons (e.g. carbon tetrachloride) and cyclic ethers (e.g. tetrahydrofuran or dioxan) and mixtures thereof. The reaction may conveniently be effected in the presence of abase such as a tertiary amine (e.g. triethylamine).

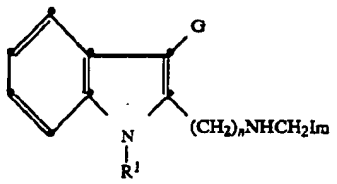
According to another general process (D), a compound of general formula (I) wherein R^3 represents a hydrogen atom, may be prepared by the reaction of a compound of formula (VI):



(VI)

or a protected derivative thereof, with formamide, at a temperature in the range of 150° to 200° C., followed where necessary by removal of any protecting groups.

According to another general process (E), a compound of general formula (I) may be prepared by reacting a compound of formula (VII):



(VII)

wherein G represents a hydrogen atom, or a protected derivative thereof, with phosgene in the presence of a Lewis acid; or by reacting a compound of formula (VII) wherein G represents an iodine or a bromine atom, or a protected derivative thereof, with carbon monoxide in the presence of a palladium (II) salt, followed where necessary by removal of any protecting groups.

According to one embodiment of process (E), a compound of formula (VII), wherein G represents a hydrogen atom, is reacted with phosgene in the presence of a Lewis acid such as anhydrous aluminium trichloride or stannic chloride. The reaction may conveniently by effected in an inert solvent such as an aromatic hydrocarbon (e.g. toluene) or a halogenated hydrocarbon (e.g. dichloromethane), or mixtures thereof, and at a temperature between ambient and 100° C.

According to another embodiment of process (E), a compound of formula (VII), wherein G represents an iodine or a bromine atoms, is reacted with carbon monoxide in the presence of a palladium (II) salt (e.g. palladium acetate or palladium chloride) and preferably in the presence of triphenylphosphine. The reaction may conveniently be effected in a solvent such as a tertiary amine (e.g. tri-n-butylamine), optionally in the presence of a co-solvent such as an ether (e.g. tetrahydrofuran) or an aromatic hydrocarbon (e.g. toluene), at a temperature in the range 100° to 150° C., and at atmospheric pressure.

According to another general process (F), a compound of general formula (I) may be converted into another compound of formula (I) using conventional techniques. Such conventional techniques include hydrogenation, alkylation and acylation using protection and deprotection where necessary.

Thus, according to one embodiment of the interconversion process (F), hydrogenation may be used to convert an alkenyl or an alkynyl substituent into an alkyl substituent, or an alkynyl into an alkenyl substituent. Hydrogenation may also be used to replace a phenylmethoxymethyl group by a hydrogen atom. Hydrogenation according to general process (F) may be effected using conventional procedures, for example, using hydrogen in the presence of a catalyst, as described above in general process (B).

The term 'alkylation' according to general process (F) includes the introduction of groups such as cycloalkyl, alkenyl or phenalkyl groups.

Thus, for example, a compound of formula (I) in which R^1 represents a C_{1-6} alkyl, C_{3-6} alkenyl, C_{3-10} alkynyl, C_{3-7} cycloalkyl, C_{3-7}cycloalkylC_{1-4} alkyl, phenyl C_{1-3} alkyl, phenylmethoxymethyl, phenoxyethyl or phenoxymethyl group may be prepared by alkylating a compound of formula (I) in which R^1 represents a hydrogen atom, or a compound in which R^3 represents a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl or phenylC_{1-3}alkyl group may be prepared by alkylating the corresponding compound of formula (I) in which R^3 represents a hydrogen atom, using conventional procedures, for example as described in published may be effected using an appropriate alkylating agent of formula R^7Z (where R^7 is the group to be introduced and Z is a leaving atom or group), preferably in the presence of a base.

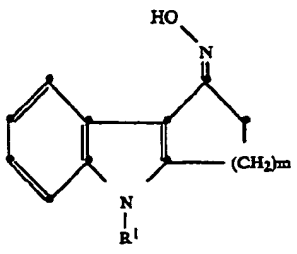
According to another embodiment of general process (F), a compound of formula (I) wherein R^1 represents $-CO_2R^5$, $-COR^5$, $-CONR^5R^6$ or $-SO_2R^5$ may be prepared by acylating or sulphonylating as appropriate, a compound of formula (I) wherein R^1 represents a hydrogen atom. The acylation/sulphonylation reactions may be effected using an appropriate acylating/sulphonylating agent according to conventional procedures, for example, as described in published European Patent Specification No. 210840.

It should be appreciated that in the above transformations it may be necessary or desirable to protect any sensitive groups in the molecule of the compound in question to avoid undesirable side reactions. For example, it may be necessary to protect the indole and/or imidazole nitrogen atoms, for example with an arylmethyl (e.g. trityl), arylmethoxymethyl (e.g. phenylmethoxymethyl), alkyl (e.g. t-butyl), alkoxymethyl (e.g. methoxymethyl), acyl (e.g. benzyloxycarbonyl) or a sulphonyl (e.g. N,N-dimethylaminosulphonyl or p-toluenesulphonyl) group.

Thus according to another general process (G), a compound of general formula (I) may be prepared by the removal of any protecting groups from a protected form of a compound of formula (I). Deprotection may be effected using conventional techniques such as those described in 'Protective Groups in Organic Synthesis' by T. S. Greene (John Wiley and sons, 1981).

For example, an arylmethoxymethyl N-protecting group may be cleaved by hydrogenolysis in the presence of a catalyst (e.g. palladium on charcoal). A trityl group may be cleaved by acid hydrolysis (e.g. using dilute hydrochloric or acetic acid). An alkoxyalkyl group may be removed using a mineral acid (e.g. dilute hydrochloric or hydrobromic acid). An acyl group may be removed by hydrolysis under acidic or basic conditions (e.g. using hydrogen bromide, dilute hydrochloric acid or sodium hydroxide). A sulphonyl group may also be removed by alkaline or acidic hydrolysis, and an N, N-dimethylaminosulphonyl group may also be removed (e.g. from an imidazole nitrogen atom) by photolysis.

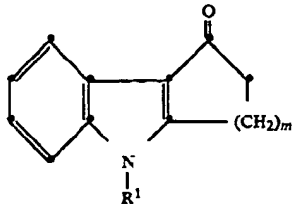
Compounds of formula (II) may be obtained by a Beckmann rearrangement of an oxime of formula (VIII):



(VIII)

wherein m represents 1 or 2, or a protected derivative thereof. The Beckmann rearrangement may be effected using conventional methods, for example by using an acid (e.g. polyphosphoric or sulphuric acid, or a mixture of hydrochloric acid, acetic anhydride and acetic acid) in an inert solvent such as an ether (e.g. dioxan), an amide (e.g. dimethylformamide) or a hydrocarbon (e.g. toluene or cyclohexane), at an elevated temperature of, for example, 50° to 120° C. Alternatively, the hydroxy group of the oxime of formula (VIII), may be converted into a leaving group such as a chloride (using, for example, phosphorus pentachloride) or a hydrocarbylsulphonate (e.g. a mesylate or a tosylate) or a trifluoroacetate group (using conventional acylation methods). Subsequent heating at a temperature of, for example, 20° to 150° C., in an inert solvent as described above, gives a compound of formula (II).

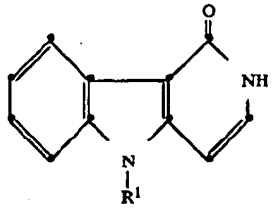
Compounds of formula (VIII) may be prepared from the corresponding tricyclic ketone of formula (IX):



(IX)

wherein m represents 1 or 2, or a protected derivative thereof using conventional methods, for example by using hydroxylamine hydrochloride in a solvent such as pyridine.

Compounds of formula (IV) may be prepared, for example, by reacting a compound of formula (X):

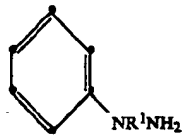


(X)

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

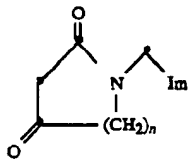
Compounds of formula (X) may be prepared by heating a compound of formula (II) wherein n represents 2, with a noble metal catalyst such as palladium, palladium oxide, platinum or nickel, at a temperature of, for example, 300° to 350° C. The catalyst may be supported on, for example, charcoal or alumina, and the reaction may optionally be carried out in the presence of an inert solvent such as an aromatic hydrocarbon (e.g. p-cymene)

Compounds of formula (V) wherein W represents a hydrogen atom and Y represents the group NH may be prepared by the reaction of a compound of formula (XI):



(XI)

or a salt thereof, with a compound of formula (XII):

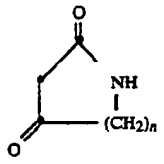


(XII)

or a protected derivative thereof, in a suitable solvent such as an aqueous alcohol (e.g. methanol), and at a temperature of, for example, from 20° to 100° C.

A protected derivative of a compound of formula (XII) may for example have the keto carbonyl group protected (e.g. as an enol ether). It will be appreciated that when a compound of formula (XII) is used in which the keto carbonyl group is protected, it may be necessary to remove the protecting group in order for reaction to occur with the compound of formula (XI). Deprotection may be carried out by conventional methods, for example by acidic hydrolysis (e.g. using dilute sulphuric or hydrochloric acid). If desired, deprotection may be effected in situ.

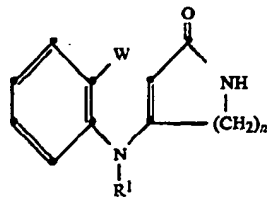
Compounds of formula (XII) may be prepared, for example, by reacting a compound of formula (XIII):



(XIII)

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

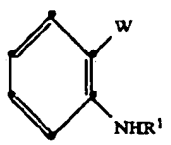
Compounds of formula (V) wherein W represents a halogen atom and Y represents a bond may be prepared, for example, by reacting a compound of formula (XIV):



(XIV)

wherein W represents a halogen atom, or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivative thereof, using the conditions described in process (A).

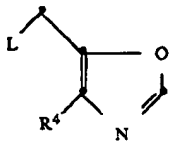
Compounds of formula (XIV) may be prepared by reacting a compound of formula (XV):



(XV)

with a compound of formula (XIII), at an elevated temperature.

Compounds of formula (VI) may be prepared, for example, by reacting a compound of formula (II), or a protected derivative thereof, with a compound of formula (XVI):

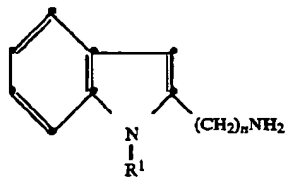


(XVI)

wherein L is as defined previously, using the conditions described in process (A).

Compounds of formula (VII) wherein G represents a halogen atom may be prepared, for example by reacting a compound of formula (VII) wherein G represents a hydrogen atom, or a protected derivative thereof, with an appropriate halogen and alkali metal halide (e.g. iodine and potassium iodide), in a suitable solvent such as an aqueous alcohol (e.g. aqueous ethanol).

Compounds of formula (VII) wherein G represents a hydrogen atom may be prepared, for example, by reacting a compound of formula (XVII):



(XVII)

or a protected derivative thereof, with a compound of formula (III) wherein L is as defined previously, or a protected derivate thereof, using the conditions described in process (A).

Compounds of formula (III) and protected derivative thereof, are either known, or may be prepared, for example, by the methods described in German Offenlegungsschrift No. 3740352.

Compounds of formula (IX) may be prepared, for example, by the method or methods analogous to that described by H. Iida et al. in *J. Org. Chem.*, 1980, 45, 2938.

Compounds of formulae (XI), (XIII), (XV), (XVI) and (XVII) are either known, or may be prepared from known compounds by conventional procedures.

Where it is desired to isolate a compound of the invention as a salt, for example a physiologically acceptable salt, this may be achieved by reacting the compound of formula (I) in the form of the free base with an appropriate acid, preferably with an equivalent amount, in a suitable solvent such as an alcohol (e.g. ethanol or methanol), an aqueous alcohol (e.g. aqueous ethanol), a halogenated hydrocarbon (e.g. dichloromethane), an ester (e.g. ethyl acetate) or an ether (e.g. tetrahydrofuran).

Physiologically acceptable salts may also be prepared from other salts, including other physiologically acceptable salts, of the compounds of formula (I) using conventional methods.

Individual enantiomers of the compounds of the invention may be obtained by resolution of a mixture of enantiomers (e.g. a racemic mixture) using conventional means, such as an optically active resolving acid; see for example 'Stereochemistry of Carbon Compounds' by E. L. Eliel (McGraw Hill, 1962) and 'Tables of Resolving Agents' by S. H. Wilen.

The methods described above for preparing the compounds of the invention may be used for the introduction of the desired groups at any stage in the stepwise formation of the required compounds, and it will be appreciated that these methods can be combined in different ways in such multi-stage processes. The sequence of the reactions in multi-stage processes should of course be chosen so that the reaction conditions used do not affect groups in the molecule which are desired in the final product.

The invention is further illustrated by the following Intermediates and Examples. All temperatures are in ° C. Thin layer chromatography (t.l.c.) was carried out on silica, and flash column chromatography (FCC) on silica (Merck 9385). solvent System A as used for chromatography denotes dichloromethane:ethanol:0.88 ammonia solution. Organic extracts were dried, where indicated, over magnesium sulphate or sodium sulphate. The following abbreviations are used: DMF - dimethylforamide; THG - tetrahydrofuran; DME - dimethoxyethane. ^{1}H-N,m.r. spectra were obtained at 250 MHz for dilute solutions in d_6-dimethyl sulphoxide.

Intermediate 1

4-(Chloromethyl)-1-(triphenylmethyl)-1H-imidazole

Thionyl chloride (0.82 g) was added over 1 min. to a stirred suspension of 1-(triphenylmethyl)-1H-imidazole-4-methanol (1.3 g) in a mixture of dichloromethane (50 ml) and DMF (1.0 ml) at 23°. The solution so obtained was stirred for 15 min. and extracted with 8% sodium bicarbonate solution (80 ml). The organic phase was washed with water (50 ml), dried and evaporated to give an oil which solidified. The solid was slurried in hexane and filtered to give the title compound (1.28 g), m.p. 139°–141°.

Intermediate 2

4-Formyl-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide

Demethylsulphamoyl chloride (0.67 ml) was added to a stirred solution of 5-propyl-1H-imidazole-4-carboxaldehyde (860 mg) and triethylamine (0.87 ml) in dry dichloromethane (10 ml) under nitrogen. The solution was heated at reflux for 24 h, allowed to cool, poured into water (50 ml) and extracted with dichloromethane (3×25 ml). The combined, dried organic extracts were evaporated to give an oil (1.9 g) which was purified by FCC eluting with ethyl acetate:hexane (1:1) to give the title compound (500 mg), m.p. 57°–58°.

Intermediate 3

4-(Hydroxymethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide

Sodium borohydride (139 mg) was added to a stirred solution of 4-formyl-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (450 mg) in absolute ethanol (5 ml) under nitrogen. After 3 h the mixture was poured into water (30 ml) and extracted with dichloromethane (3×15 ml). The combined, dried organic extracts were evaporated to give a solid (425 mg) which was triturated with ether (2×10 ml) to give the title compound (350 mg), m.p. 86°–88°.

Intermediate 4

4-(Chloromethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide

A solution of thionyl chloride (0.12 ml) in dry dichloromethane (1.2 ml) was added dropwise to a cold (0°) stirred solution of 4-(hydroxymethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (340 mg) in dry dichloromethane (7.5 ml) under nitrogen. After 1.5 h the solution was washed with 8% sodium bicarbonate solution (2×15 ml) and the aqueous phase was extracted with dichloromethane (2×10 ml). The combined organic extracts were washed with water (15 ml), dried and evaporated to give the title compound (180 ml) as an oil, t.l.c. (ethyl acetate) Rf 0.68.

Intermediate 5

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one (1.7 g) and hydroxylamine hydrochloride (1.925 g) in pyridine were heated at 60° for 18 h and cooled. The reaction mixture was evaporated in vacuo to a residue to which was added 8% sodium bicarbonate (150 ml). Extraction with ethyl acetate (300 ml) produced a suspension in the organic layer; this layer and associated solid was separated from the aqueous layer. The aqueous layer was re-extracted with ethyl acetate (250 ml). The combined organic extracts (and suspended solid) were evaporated to a residue, boiled with a mixture of ethanol (150 ml) and methanol (150 ml) and cooled to ca. 50°. The residue was adsorbed from this solution on to FCC silica and applied to an FCC column. Elution with ethyl acetate/3–10% methanol provided the title compound (1.69 g), m.p. 219°–224° (decomp.).

Intermediate 6

2,3,4,5-Tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one

3,4-Dihydro-4-methylcyclopent[b]indol-1(2H)-one oxime (1.53 g), polyphosphric acid (450 g) and dioxan (15 ml) were heated at 100°–120° for 2.2 h under nitrogen. The reaction mixture was cooled, and treated with 2N sodium carbonate solution (1 l). The suspension was extracted with ethyl acetate (4×400 ml) and the combined extracts were dried. Evaporation gave a solid (1.43 g) which was recrystallised from ethyl acetate/cyclohexane. This solid was purified by FCC, eluting with System A (200:10:1) to give a solid (1.26 g) which was recrystallised from ethanol to provide the title compound (960 mg), m.p. 234°–238°.

Intermediate 7

3,4,5,6,-Tetrahydro-6-methylazepino[4,3-b]indol-1(2H)-one

1,2,3,9-Tetrahydro-9-methyl-4H-carbazol-4-one oxime (24 g) and polyphosphoric acid (600 g) in dioxan (500 ml) were treated according to the method described for Intermediate 6. The solid (22 g) obtained by evaporation of the organic extracts was recrystallised from ethyl acetate (300 ml) to give a solid (19.2 g). This was purified by FCC eluting with System A (200:8:1) to give the title compound (5.5 g), m.p. 212°–215°.

Intermediate 8

5,6-Dihydro-4-(phenylamino)-1(2H)-pyridinone

A mixture of 2,4-dioxopiperidine (1.13 g) and aniline (930 mg) was heated at 120° under a stream of nitrogen for 15 min. The resultant solid was triturated with ether and filtered off to give the title compound (1.74 g), m.p. 235°–238°.

Intermediate 9

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one

A solution of 5,6-dihydro-4-(phenylamino)-1(2H)-pyridinone (1.5 g) and palladium acetate (150 mg) in dry DMF (50 ml) was treated with cupric acetate (3.2 g) and the resulting mixture was heated under nitrogen at 120°–130° for 1.5 h. The mixture was then concentrated in vacuo to give a solid which was triturated with 2N hydrochloric acid (250 ml). The acid was decanted, and the remaining solid was extracted with ethyl acetate for 18 h. The decanted acid was basified with 2N sodium hydroxide and extracted with ethyl acetate (3×100 ml). These organic extracts were combined with the previous ethyl acetate extracts and adsorbed onto silica. Purification by FCC eluting with System A (100:8:1) gave the title compound (874 mg), m.p. 212°–215°.

Intermediate 10

2,3,4,5-Tetrahydro-5-[(phenylmethoxy)methyl]-1H-pyrido[4,3-b]indol-1-one

a solution of 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (1.12 g) in dry DMF (60 ml) was treated with sodium hydride (60% dispersion in oil; 480 mg) and the resulting mixture was stirred under nitrogen until effervescence ceased. The mixture was then cooled to 0° and benzyl (chloromethyl) ether (10% w/v solution in DMF; 0,835 ml) was added over 10 min. Stirring was continued for a further 5 min and then water (10 ml) was added. The reaction mixture was concentrated in vacuo to give an oil which was dissolved in ethyl acetate (100 ml) and washed with water (3×100 ml). The organic phase was dried and adsorbed onto FCC silica. Purification by FCC eluting with System A (150:8:1) gave the title compound 1.1 g), m.p. 133°–135°.

Intermediates 11 to 14 were prepared in a similar manner to Intermediate 10, i.e. by treating 2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one with sodium hydride followed by an appropriate alkylating agent. Isolation and purification of the products were as described for Intermediate 10 unless otherwise stated.

Intermediate 11

5-Ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (931 mg) was treated with sodium hydride (60% dispersion

in oil; 400 mg) and was then stirred with ethyl iodide (10% v/v solution in DMF; 4 ml) to give the title compound (758 mg), m.p. 203°–204.5°.

Intermediate 12

2,3,4,5-Tetrahydro-5-(1-methylethyl)-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (931 mg) was treated with sodium hydride (73% dispersion in oil; 328 mg) and was then stirred with 2-bromopropane (615 mg) at room temperature for 72 h. Purification by FCC eluting with System A (200:8:1) gave a foam (324 mg) which was further purified by recrystallisation from ethyl acetate: hexane (1:1) to give the title compound (249 mg), t.l.c. (System A, 100:8:1) Rf 0.58.

Intermediate 13

2,3,4,5-Tetrahydro-5-(phenylmethyl)-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (559 mg) was treated with sodium hydride (73% dispersion in oil; 197 mg) and was then stirred with benzyl bromide (513 mg) at room temperature for 30 min. Purification by FCC eluting with dichloromethan: ethanol (80:1) gave the title compound (347 mg), m.p. 209°–212°.

Intermediate 14

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one

2,3,4,5-Tetrahydro-1H-pyrido[4,3-b]indol-1-one (950 mg) was treated with sodium hydride (60% dispersion in oil; 408 mg) and was then stirred with cyclopentahemethanol (methane sulphonate) (909 mg) at room temperature for 7 days. The solid (570 mg) obtained by FCC was further purified by slow evaporation form a solution in methanol to give the title compound, m.p. 179°–181°.

Intermediate 15

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of triphenylmethyl chloride (3.36 g) in dry DMF (40 ml) was added dropwise to a stirred solution of 2,3,4,5-tetrahydro-2-](5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (2.8 g) in dry DMF (50 ml) containing triethylamine (1.52 g). When addition was complete the mixture was stirred overnight. The mixture was then poured into water (1000 ml) and the resulting suspension was extracted with ethyl acetate (3×300 ml). The combined organic extracts were washed with water (2×500 ml), dried and concentrated onto silica. FCC eluting with System A (100:8:1) gave the title compound (4.3 g), m.p. 235°–236°.

Intermediate 16

2,3,4,5-Tetrahydro-5-methyl-2-[[1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (0.3 g) and sodium hydride (80% dispersion in oil; 0.05 g) in dry DMF (5 ml) was stirred under nitrogen at 50° until hydrogen evolution ceased (ca. 0.5 h). The mixture was cooled to 40° and a solution of 4-(chloromethyl)-1-(triphenylmethyl)-1H-imidazole (0.53 g) in dry THF (3 ml) was added. The mixture was stirred at 40° to 23° over 2 h, poured into water (100 ml) and extracted with dichloromethane (3×100 ml). The dried organic phase was evaporated to give a semi-solid which was purified by FCC eluting with dichloromethane:ethyl acetate:triethylamine (50:50:1) to give a solid. This was slurried in hexane and filtered to give the title compound (0.37 g), m.p. 205°–210° (decomp.).

Intermediate 17

2,5-Dihydro-5-methyl-1H-pyrido[4,3, -b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (500 mg) and 10% palladium oxide on carbon catalyst (50% aqueous paste; 250 mg) was heated at 320° for 10 min. The cooled solid was triturated with ethanol (ca. 100 ml), filtered and the resulting filtrate was evaporated to give the title compound (470 mg), m.p. 242.5°.

Intermediate 18

2,5-Dihydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (73% dispersion in oil; 80 mg) was added to a stirred suspension of 2,5-dihydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (440 mg) in dry dimethoxyethane (25 ml) under nitrogen and the mixture was heated at 50° for 6 h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (910 mg) was then added, and stirring was continued at 50° for 20 h. Water (4.5 ml) and acetic acid (4.5 ml) were added and the solution was heated at reflux for 5 h. The mixture was poured into 8% sodium bicarbonate solution (80 ml) and extracted with dichloromethan:ethanol (10:1; 3×40 ml). The combined, dried organic extracts were evaporated to give a solid (ca. 1.5 g) which was purified by FCC eluting with System A (100:10:1) to give the free base of the title compound as a solid (348 mg). A sample of this solid (100 mg) was dissolved in absolute ethanol (20 ml) and treated with a solution of maleic acid (40 mg) in absolute ethanol (1 ml). The solvent was removed in vacuo and the residue was triturated with dry ether (3×20 ml) to give a solid (115 mg) which as re-crystallised from methanol-ethyl acetate to give the title compound (40 mg), m.p., 166°–168°.

Intermediate 19

5,6-Dihydro-4-methoxy-1-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-2(1H)-pyridinone

Sodium hydride (80% dispersion in oil; 360 mg) was suspended in dry DME (50 ml) under nitrogen and 5,6-dihydro-4-methoxy-2(1H)-pyridinone (1.27 g) in dry DME (20 ml) was added slowly. The resulting suspension was stirred at 20° for 1 h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (3.72 g) in dry DME (50 ml) was added, and after the initial reaction had subsided the mixture was heated to 50° for 4 h and then cooled. Methanol (5 ml) was added dropwise, and solvent was removed invacuo. 8% Aqueous sodium bicarbonate solution (300 ml) was added to the residue and the resulting solution was extracted with dichloromethane (2×300 ml), dried and evaporated in vacuo to leave an oil which was purified by FCC eluting with System A (200:8:1) to give the title compound (2.84 g), m.p. 181°–184°.

Intermediate 20

2,4-Dioxo-1-[(5-methyl-1H-imidazol-4-yl)methyl]-piperidine

To a solution of 5,6-dihydro-4-methoxy-1-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4yl]methyl]-2(1H)-pyridinone (500 mg) in THF (4 ml) was added hydrochloric acid (5M; 1 ml), and the mixture was stirred at 50° for 1 h. The solvent was removed in vacuo, triethylamine (1 ml) was added, and the mixture was again evaporated to dryness. FCC of the residue eluting with ethyl acetate:methanol:triethylamine (8:4:1) gave the title compound (139 mg), m.p. 100°-106° (decomp.).

Intermediate 21

5,6-Dihydro-1-](5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone

2,4-Dioxo-1-[(5-methyl-1H-imidazol-4-yl)methyl]-piperidine (200 mg) was dissolved in ethanol (2 ml) and N-methylphenylhydrazine (26 mg) was added. The mixture was stirred for 1 h and the solvent was removed in vacuo. The residue was purified by FCC eluting with system A (75:8:1) to give the title compound (24 mg) as a solid, t.l.c. (System A, 75:8:1) Rf 0.27.

Intermediate 22

N,N,5-Trimethyl-4-[[(trimethylsilyl)oxy]methyl]-1H-imidazole-1-sulphonamide

A suspension of 4-(hydroxymethyl)-5-methylimidazole hydrochloride (14.9 g) in dry dichloromethane (500 ml) containing triethylamine (50 g) was treated with trimethylsilyl chloride (21.7 g) and the reaction mixture was stirred at room temperature overnight. Dimethylsulphamoyl chloride (14.3 g) was added and the reaction mixture was again stirred at room temperature overnight. The resulting suspension was filtered and the collected solid was washed with dichloromethane (100 ml). The filtrate was concentrated onto silica and purification by FCC eluting with hexane:ether (4:1) gave the title compound as an oil (7.2 g), t.l.c. (ether) Rf 0.5.

Intermediate 23

4-(Hydroxymethyl)-N,N5-trimethyl-1H-imidazole-1-sulphonamide

A solution of N,N,5-trimethyl-4-[[(trimethylsilyl)oxy]methyl]-1H-imidazole-1-sulphonamide (2.59 g) in dry THF (50 ml) was treated with a solution of tetrabutylammonium fluoride (1M solution in THF; 10 ml). and the THF was immediately removed in vacuo. The residue was partitioned between water (100 ml) and dichloromethane (100 ml) and the aqueous layer was extracted with dichloromethane (100 ml). The combined, dried organic fractions were concentrated to give the title compound (1.63 g) as a solid, m.p. 134°-136°.

Intermediate 24

4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide

A suspension of 4-(hydroxymethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (2.86 g) in dry dichloromethane (200 ml) containing DMF (0.5 ml) was treated dropwise with a solution of thionyl chloride (1.178 g) in dichloromethane (10 ml). The reaction mixture was cooled in ice during the addition and blanketed with nitrogen. When addition was complete (ca. 5 min), stirring was continued at 0° for a further 30 min. Water (200 ml) was then added and the organic phase was separated, washed with 8% sodium bicarbonate (100 ml), dried and concentrated to give the title compound (2.3 g) as a solid, m.p. 115°-118°.

Intermediate 25

5,6-Dihydro-4-[(2-iodophenyl)methylamino]-2(1H)-pyridinone

A mixture of 2-iodo-(N-methyl)aniline (1.17 g) and 2,4-dioxopiperidine (565 mg) was heated under a stream of nitrogen for 7 h at 110°-120°. After cooling the reaction mixture was dissolved in methanol and the solution was adsorbed onto FCC silica. Purification by FCC eluting with System A (150:8:1) gave the title compound (1.03 g), m.p. 163°-164°.

Intermediate 26

N,N5-Trimethyl-4-[1,2,3,6-tetrahydro-4-[(2-iodophenyl)-methylamino]-6-oxo-1-pyridinyl]methyl-1H-imidazole-1-sulphonamide

A suspension of 5,6-dihydro-4-[(2-iodophenyl)methylamino]-2(1H)-pyridinone (984 mg) in dry DME (50 ml) was treated with sodium hydride (60% dispersion in oil; 140 mg), and the mixture was stirred under nitrogen for 6 h. 4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (832 mg) was then added and the resulting mixture was stirred at 60° overnight. After cooling the reaction mixture was poured into water (100 ml), and the mixture was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated, and the resultant solid was purified by FCC eluting with System A (150:8:1) to give the title compound (712 mg), t.l.c. (System A, 150:8:1) Rf 0.41.

Intermediate 27

N,N,5-Trimethyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide

A solution of dimethylsulphamoyl chloride (0.107 ml) in dry dichloromethane was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (0.294 g) and triethylamine (0.2 ml) in dry dichloromethane (30 ml) under nitrogen, and the mixture was heated at reflux for ca. 24 h. After cooling the solution was concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give an oil. This oil was triturated with ether to give a solid which was further purified by slow evaporation from a solution in ethyl acetate to give the title compound (122 mg), m.p. 194°-196°, t.l.c. (System A, 100:8:1) Rf 0.43.

Intermediate 28

Phenylmethyl 5-methyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2yl)methyl]-1H-imidazole-1-carboxylate

A solution of benzyl chloroformate (0.28 ml) in dichloromethane (10 ml) was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1one (294 mg) and triethylamine (0.4 ml) in dichloromethane (30 ml) at 20° under nitrogen, and the mixture was stirred overnight. It was then concentrated onto FCC silica

and purified by FCC eluting with System A (200:8:1) to give the title compound (62 mg), t.l.c. (System A, 100:8:1) Rf 0.50.

Intermediate 29

2,3,4,5-Tetrahydro-2-[[1-(methoxymethyl)-5-methyl-1H-imidazol-4-yl]-methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one and
2,3,4,5-Tetrahydro-2-[[1-(methoxymethyl)-4-methyl-1H-imidazol-5yl]methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one

A solution of chloromethyl methyl ether (0.26 ml) in dichloromethane (10 ml) was added to a stirred solution of 2,3,4,5-tetrahydro-5-methyl-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (500 mg) and triethylamine (0.49 ml) in dichloromethane (50 ml) at 20° under nitrogen, and the solution was stirred for 4 days. It was then partitioned between dichlormethane (50 ml) and sodium bicarbonate solution (2×50 ml). The organic extract was dried, concentrated onto FCC silica, and then purified by FCC elution with System A (100:8:1) to give the title compounds (139 mg). A portion of the title compound (64 mg) was taken up in hot ethyl acetate and purified by slow evaporation from ethyl acetate to give the title compounds.

Analysis Found: C67.3; H,6.9; N,16.5; $C_{19}H_{22}N_4O_2$ requires C,67.4; H,6.6; N,16.6%.

Intermediate 30

2,3,4,5-Tetrahydro-5-methyl-2-[(4-methyloxazol-5-yl)methyl]-1H-pyrido[4,3-b]-indol-1-one

Sodium hydride (60% dispersion in oil; 600 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (1.5 g) in dry DME (150 ml) and then the mixture was stirred at 60° for 5 h under nitrogen. 5-Chloromethyl-4-methyloxazole (1.2 g) was added and the mixture was stirred overnight. A further quantity of sodium hydride (60% dispersion in oil; 600 mg) was added and the mixture was stirred at 60° for 4 h, then cautiously treated with water (100 ml). The mixture was extracted with dichloromethane containing methanol (ca. 1%) (3×100 ml) and the combined extracts were evaporated. The residue was purified by FCC eluting with System A (100:8:1) to give the title compound (300 mg) as a solid, t.l.c. (System A, 100:8:1) Rf 0.4.

Intermediate 31

N-[(1-Methyl-1H-indol-2-yl)ethyl]trifluoroacetamide

A solution of 2-(1-methyl-1H-indol-2-yl)ethanamine (3.48 g) in dry dichloromethane (50 ml) containing triethylamine (2.53 g) was cooled in an ice bath, and trifluoroacetic anhydride (5.25 g) was added dropwise over 15 min. The mixture was then allowed to warm to room temperature and stirred for an additional 3 h. After this time the reaction mixture was poured into water (100 ml), the organic phase was separated, and the aqueous phase was washed with dichloromethane (2×50 ml). The combined, dried organic extracts were concentrated onto FCC silica and purification by FCC eluting with ether gave the title compound (4.2 g) as a solid. A sample of this compound was further purified by slow evaporation from a solution in dichloromethane, m.p. 124°–126°.

Intermediate 32

N,N,5-Trimethyl-4-[[(1-methyl-1H-indol-2-yl)-N-trifluoroacetylamino]-ethyl]imidazole-1-sulphonamide

A solution of N-[(1-methyl-1H-indol-2-yl)ethyl]trifluoroacetamide (2.7 g) in dry DMF (100 ml) was treated with sodium hydride (60% dispersion in oil; 480 mg), and the mixture was stirred at room temperature for 30 min. 4-(Chloromethyl)-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (2.37 g) was then added and the mixture was stirred at room temperature overnight. After this time the reaction mixture was poured into water (500 ml) and the resulting suspension was extracted with ethyl acetate (2×100 ml). The combined organic extracts were washed with water (5×250 ml), dried and adsorbed onto FCC silica. Purification by FCC eluting with System A (150:8:1) gave the title compound (1.9 g), m.p. 156°–158°.

Intermediate 33

4-[[[(1-Methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H -imidazole-1-sulphonamide

A mixture of N,N,5-trimethyl-4[[(1-methyl-1H-indol-2-yl)-N-trifluoro-acetylamino]ethyl]imidazole-1-sulphonamide (260 mg), methanol (10 ml) and saturated aqueous potassium carbonate solution (5 ml) was heated to 60° for 1.5 h. After cooling the mixture was poured into water (50 ml) and the mixture was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (143 mg) as an oil, t.l.c. (System A, 100:8:1) Rf 0.51.

Intermediate 34

4-[[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]trifluoroacetylamino]-methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide

A solution of 4-[[[(1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (471 mg) in methanol (25 ml) containing potassium carbonate (138 mg) was treated with a solution of iodine (254 mg) and potassium iodide (166 mg) in water (30 ml) over 30 min. When addition was complete the reaction mixture was stirred for a further 2 h. After this time additional methanol was removed in vacuo and the resulting suspension was extracted with ethyl acetate (3×25 ml). The combined organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (367 mg), m.p. 141°–143°.

Intermediate 35

4-[[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide

4-[[[(3-Iodo-1-methyl-1H-indol-2-yl)ethyl]trifluoroacetylamino]-methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (199 mg) was deprotected according to the method described in Intermediate 33 to give the title compound (50 mg) as an oil, t.l.c. (System A, 150:8:1) Rf 0.51.

EXAMPLE 1

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

A mixture of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (0.6 g) and ca. 78% sodium hydride dispersion in mineral oil (0.109 g) in dry DMF (15 ml) was stirred under nitrogen at 50° until hydrogen evolution ceased (ca. 1.5 h). The mixture was cooled to 40° and a solution of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 g) in dry THF (15 ml) was added. The reaction was then stirred at 40° for 3 h, at 20° for 16 h and a further portion of 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.12 g) in dry THF (15 ml) was added. The resulting mixture was heated at 40° for 3 h, quenched with water (20 ml) and acetic acid (20 ml), and heated at 100° for 2 h. The mixture was then concentrated in vacuo to ca. 60 ml, diluted with 1M hydrochloric acid (40 ml) and washed with ethyl acetate (3×50 ml). The organic phase was discarded and the acidic aqueous phase was basified (pH9) with potassium carbonate and extracted with ethyl acetate: ethanol (20:1, 3×100 ml). The extracts were combined, dried and evaporated to give a brown gum (ca. 1 g). This gum was adsorbed onto silica and purified by FCC eluting with System A (100:8:1) to give a pale brown solid (0.8 g) m.p. 238°–240° (decomp). This solid was dissolved in a mixture of hot ethanol and methanol (1:1; 100 ml) and treated with an ethanolic solution of maleic acid (318 g). The resulting solution was concentrated to ca. 20 ml and diluted with dry diethyl ether (ca. 8 ml) to precipitate the title compound (0.75 g) as an off-white solid, m.p. 160°–162°.

Analysis Found: C,61.6; H,5.5; N,13.6; $C_{17}H_{18}N_4O.C_4H_4O_4$ requires C,61.5; H,5.4; N,13.8%.

EXAMPLE 2

3,4,5,6-Tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one maleate

3,4,5,6-Tetrahydro-6-methylazepino[4,3-b]indol-1-(2H)-one (0.64 g) was treated with sodium hydride (ca. 75–80% dispersion in oil; 0.108 g) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole as described in Example 1. The reaction mixture was then poured into water (300 ml) and extracted with dichloromethane (4×250 ml). The combined, dried organic extracts were evaporated to give a semi-solid (ca. 1.8 g) which was purified by FCC eluting with System A (200:8:1) to give a gum (0.7 g). The gum (0.7 g) was dissolved in a mixture of acetic acid, THF and water (1:1:1; ca. 70 ml) and heated on a steam bath for 1 h. Work-up as described in Example 1 gave a gum (0.22 g) which was purified by FCC eluting with System A (200:8:1) to give a solid (0.11 g). Maleate formation gave a gum which was dried in vacuo to give a foam which was triturated with a mixture of ether and ethanol (50:1; ca. 25 ml) to give the title compound (0.145 g) as a solid, m.p. 132°–133°.

^{1}H-N.m.r. indicated 0.39 mol of ethanol present. Water Analysis Found 0.583% w/w=0.14 mol H_2O. Analysis Found: C,61.4; H,5.7; N,12.6; $C_{18}H_{20}N_4O.C_4H_4O_4.0.39EtOH$. 0.14 H_2O requires C,61.4; H,6.0; N,12.6%.

EXAMPLE 3

2,3,4,5-Tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-5-[(phenylmethoxy)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tetrahydro-5-[(phenylmethoxy)methyl]-1H-pyrido[4,3-b]indol-1-one (920 mg) in dry DME (75 ml) was treated with sodium hydride (60% dispersion in oil; 180 mg) under nitrogen and the reaction mixture was stirred at 60° for 6 h.

4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.11 g) was then added and the mixture was stirred at 60° overnight. Acetic acid (10 ml), water (10 ml) and THF (10 ml) were then added and the resulting solution was heated at reflux for 6 h. After cooling, 2N sodium hydroxide (100 ml) was added and the resulting suspension was extracted with dichloromethane (3×100 ml). The combined, dried organic extracts were adsorbed onto FCC silica, and FCC eluting with System A (150:8:1) gave the free base of the title compound (1.08 g) as a foam. A small amount of this compound (200 mg) was dissolved in methanol (30 ml) and the resulting solution was treated with maleic acid (58 mg). The solution was heated for 10 min., cooled, and dry ether was added to precipitate the title compound (170 mg), m.p. 165°–168°.

Water Analysis Found 0.22% w/w=0.06 mol H_2O. Analysis Found: C,64.5; H,5.6; N,10.7; $C_{24}H_{24}N_4O.C_4H_4O_4$. 0.06 H_2O requires C,65.0; H,5.5; N,10.8%.

Examples 4 to 7 were prepared in a similar manner to Example 3.

EXAMPLE 4

5-Ethyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

5-Ethyl-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (500 mg) was treated with sodium hydride (60% dispersion in oil; 138 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (927.5 mg) to give the free base of the title compound (320 mg) as a solid. Maleate formation gave the title compound (380 mg), m.p. 175.5°–177°.

Analysis Found: C,62.1; H,5.7; N,13.0; $C_{18}H_{20}N_4O.C_4H_4O_4$ requires C,62.2; H,5.7; N,13.2%.

EXAMPLE 5

2,3,4,5-Tetrahydro-5-(1-methylethyl)-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

2,3,4,5-Tetrahydro-5-(1-methylethyl)-1H-pyrido[4,3-b]indol-1-one (228 mg) was treated with sodium hydride (60% dispersion in oil; 60 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (371 mg) to give the free base of the title compound (180 mg) as a solid. Maleate formation gave the title compound (172 mg), m.p. 203°–205°.

Analysis Found: C,62.6; H,6.0; N,12.6; $C_{19}H_{22}N_4O.C_4H_4O_4$ requires C,63.0; H,6.0; N,12.8%.

EXAMPLE 6

2,3,4,5-Tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one maleate monohydrate

2,3,4,5-Tetrahydro-5-(phenylmethyl)-1H-pyrido[4,3-b]indol-1-one (960 mg) was treated with sodium hydride (73% dispersion in oil; 132 mg) and was then

stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (1.3 g). The free base of the title compound (571 mg) was obtained as a solid by FCC eluting with System A (175:8:1). Maleate formation gave the title compound (420 mg), m.p. 198°–200°, t.l.c. (System A, 100:8:1) Rf 0.3.

EXAMPLE 7

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

5-(Cyclopentylmethyl)-2,3,4,5-tetrahydro-1H-pyrido[4,3-b]indol-1-one (200 mg) was treated with sodium hydride (60% dispersion in oil; 60 mg) and was then stirred with 4-(chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (280 mg). The free base of the title compound was obtained as a solid (96 mg) by FCC eluting with System A (200:8:1). Maleate formation gave the title compound (60 mg), m.p. 81°–83°, t.l.c. (System A, 100:8:1) Rf 0.20.

EXAMPLE 8

2,3,4,5-Tetrahydro-5-methyl-2-[(5-propyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (60% dispersion in oil; 25 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (124 mg) in dry DME (5 ml) under nitrogen. The mixture was heated at 50° for 7 h and then treated with a solution of 4-(chloromethyl)-N,N-dimethyl-5-propyl-1H-imidazole-1-sulphonamide (165 mg) in dry DME (3 ml) and stirring was continued at 50° for 20 h. 2N Hydrochloric acid (5 ml) was added and the solution was heated at reflux for 6 h. The solution was poured into 8% sodium bicarbonate solution (50 ml) and extracted with dichloromethane (3×25 ml). The combined, dried organic extracts were evaporated to give a solid (200 mg) which was purified by FCC eluting with System A (200:10:1) to give the free base of the title compound (58 mg) as a solid. This was dissolved in warm absolute ethanol (5 ml) and treated with a solution of maleic acid (21 mg) in ethanol (0.5 ml). The solvent was removed in vacuo and the residue was crystallised from ethanol:ether to give the title compound (58 mg), m.p. 137°–138°.

Analysis Found: C,62.7; H,5.9; N,12.4; $C_{19}H_{22}N_4O.C_4H_4O_4$ requires C,63.0; H,6.0; N,12.8%.

EXAMPLE 9

2,3,4,5-Tetrahydro-N,N-dimethyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide maleate

A solution of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (261 mg) in dry DMF (25 ml) was treated with sodium hydride (60% dispersion in oil; 30 mg) and the mixture was stirred at room temperature under nitrogen for 15 min. N,N-Dimethylcarbamoyl chloride (1M solution in DMF; 1 ml) was then added and the solution was stirred at room temperature for an additional 15 min. Water (1 ml) was cautiously added, and the reaction mixture was then poured into water (100 ml). The resulting mixture was extracted with ethyl acetate (2×50 ml) and the combined organic extracts were washed with water (2×100 ml) and concentrated to give an oil. The oil was dissolved in a mixture of water (10 ml), glacial acetic acid (10 ml) and THF (10 ml) and the solution was heated at reflux for 1.5 h. After cooling the solution was basified by addition of 2N sodium hydroxide (100 ml), and the resulting mixture was extracted with ethyl acetate (2×75 ml). The combined, dried organic extracts were adsorbed onto FCC silica and the free base of the title compound (110 mg) was obtained by FCC eluting with System A (100:8:1) as a solid. This was dissolved in dry methanol (10 ml) and heated with maleic acid (36 mg) on a steam bath for 5 min. On cooling, dry ether (3 ml) was added to precipitate the title compound (105 mg), m.p. 161°–163°.

Water Analysis Found 1.85% w/w=0.49 mol H_2O. Analysis Found: C,5.78; H,5.4; N,14.3; $C_{19}H_{21}N_5O_2.C_4H_4O_4$. 0.49 H_2O requires C,68.0; H,5.5; N,14.7%.

Examples 10, 11 and 12 were prepared in a similar manner to Example 9 unless otherwise stated.

EXAMPLE 10

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(methylsulphonly)-1H -pyrido[4,3-b]indol-1-one maleate

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (261 mg) was treated with sodium hydride (60% dispersion in oil; 30 mg) and was then stirred with methanesulphonyl chloride (1M solution in dry DMF; 1 ml) for 45 min. Deprotection, work-up and purification gave the free base of the title compound (60 mg) as a solid. Maleate formation gave the title compound (57 mg), m.p. 152°–155°.

Analysis Found: C,53.2; H,4.7; N,11.7; $C_{17}H_{18}N_4O_3S.C_4H_4O_4$ requires C,53.2; H,4.7; N,11.8%.

EXAMPLE 11

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (522 mg) and potassium carbonate (276 mg) in dry acetone (75 ml) was treated with propargyl bromide (1M solution in acetone; 2 ml) and the mixture was heated at reflux overnight. After cooling, excess acetone was removed in vacuo to give an oil which was partitioned between water (100 ml) and ethyl acetate (100 ml). The aqueous phase was washed with ethyl acetate (50 ml) and the combined organic extracts were concentrated in vacuo. Deprotection, work-up and purification gave the free base of the title compound (100 mg) as a solid. Maleate formation gave the title compound (89 mg), m.p. 202°–205°, t.l.c. (System A, 100:8:1) Rf 0.29.

EXAMPLE 12

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propenyl)-1H-pyrido[4,3-b]indol-1-one maleate

2,3,4,5-Tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (1.0 g) was treated with sodium hydride (60% dispersion in oil; 114 mg) and was then stirred with allyl bromide (460 mg) for 1 h. Deprotection, work-up and purification gave the free base of the title compound (380 mg) as a solid. Maleate formation gave the title compound (160 mg), t.l.c. (System A, 100:8:1) Rf 0.3.

Analysis Found: C,63.2; H,5.5; N,12.5; $C_{19}H_{20}N_4O.C_4H_4O_4$ requires C,63.3; H,5.5; N,12.8%.

EXAMPLE 13

5-Cyclopentyl-2,3,4,5-tetrahydro-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

A solution of 2,3,4,5-tetrahydro-2-[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (523 mg) in dry DMF (30 ml) was treated with sodium hydride (60% dispersion in oil; 46 mg) and stirred for 15 min. at 21° under nitrogen. Cyclopentyl bromide (298 mg) was then added dropwise, and the mixture was stirred for 1 h and then heated at reflux for 4 h. The solution was left at 21° for 2 days, and then treated with a mixture of acetic acid (7 ml), water (7 ml) and THF (8 ml). The resulting solution was heated at reflux for 4 h, then basified with 2N sodium hydroxide and extracted with dichloromethane (3×25 ml). The combined extracts were washed with water (2×50 ml), concentrated in vacuo and purified by FCC eluting with System A (100:8:1) to give the free base of the title compound (42 mg) as a solid. Maleate formation gave the title compound (38 mg), m.p. 180° (decomp.), t.l.c. (System A, 100:8:1) Rf 0.3.

EXAMPLE 14

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one maleate

A solution of 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-(2-propyl)-1H-pyrido[4,3-b]indol-1-one (248 mg) in a mixture of ethanol (20 ml) and 2N hydrochloric acid (0.5 ml) was hydrogenated at room temperature and atmospheric pressure over a pre-reduced 10% palladium oxide on carbon catalyst (50% aqueous paste; 50 mg). The mixture was filtered and evaporated in vacuo. The residue was basified with 2N sodium hydroxide (10 ml) and extracted with dichloromethane (3×20 ml). The combined organic extracts were washed with water (30 ml) and evaporated to give the free base of the title compound (258 mg) as a solid. Maleate formation gave the title compound 345 mg), t.l.c. (System A, 100:8:1) Rf 0.4.

Water Analysis Found 1.13% w/w≡0.28 mol H_2O. Analysis Found: C,62.1; H,5.9; N,12.5; $C_{19}H_{22}N_4O.C_4H_4O_4$ 0.28 H_2O requires C,62.2; H,6.0; N,12.6%.

EXAMPLE 15

2,3,4,5-Tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido-[4,3-b]indol-1-one maleate

A suspension of 2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)-methyl]-5-[phenyl(methoxymethyl)]-1H-pyrido[4,3-b]indol-1-one (400 mg) in ethanol (20 ml) and glacial acetic acid (5 ml) was hydrogenated overnight at room temperature and atmospheric pressure over a pre-reduced 10% palladium oxide on carbon catalyst (50% aqueous paste; 100 mg). The reaction mixture was filtered and the residue was washed with ethanol (100 ml). The filtrate was concentrated in vacuo to give an oil, to which was added 2N sodium hydroxide (50 ml). The resulting suspension was extracted with dichloromethane (2×50 ml) and the combined, dried organic extracts were evaporated to give a solid. This was purified by FCC eluting with System A (75:8:1) to give the free base of the title compound as a solid (240 mg) which was then dissolved in dry methanol (50 ml). Maleate formation gave the title compound (261 mg), t.l.c. (System A, 75:8:1) Rf 0.2

Analysis Found: C,60.3; H,5.2; N,13.8; $C_{16}H_{16}N_4O.C_4H_4O_4$ requires C,60.6; H,5.1; N,14.1%.

EXAMPLE 16

2,3,4,5-Tetrahydro-5-methyl-2-[(1,5-dimethyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one maleate

Sodium hydride (73% dispersion in oil; 40 mg) was added to a stirred suspension of 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (300 mg) in dry DMF (3 ml) under nitrogen. After 30 min. the suspension was cooled to 0° and iodomethane (0.076 ml) was added dropwise. The mixture was allowed to reach room temperature, stirred for 1.5 h, then poured into water (30 ml) and extracted with dichloromethane (3×15 ml). The combined, dried organic extracts were evaporated to give an oil (ca. 545 mg) which was purified by FCC eluting with System A (200:8:1) to give a solid (95 mg). A portion of this material (90 mg) was dissolved in absolute ethanol (3 ml) and treated with a solution of maleic acid (35 mg) in absolute ethanol (1 ml). The solvent was removed in vacuo and the residue was triturated with dry ether (3×5 ml) to give the title compound (122 mg), m.p. 178°–180°.

Analysis Found: C,62.1; H,5.7; N,13.1; $C_{18}H_{20}N_4O.C_4H_4O_4$ requires C,62.3; H,5.7; N,13.2%.

EXAMPLE 17

2,3,4,5-Tetrahydro-2-[(1H-imidazol-4-yl)methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one dimaleate

A solution of 2,3,4,5-tetrahydro-5-methyl-2-[[(1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (0.22 g) in a mixture of acetic acid, THF and water (1:1:1; 10 ml) was heated on a steam bath for 30 min. The suspension so obtained was diluted with 1M hydrochloric acid (20 ml) and washed with ethyl acetate (3×20 ml). The acidic aqueous phase was basified with solid sodium carbonate and extracted with dichloromethane:methanol (9:1; 3×20 ml). The combined, dried organic extracts were evaporated to give a foam which was dissolved in methanol (5 ml) and treated with a solution of maleic acid (0.15 g) in methanol (5 ml). The clear solution was evaporated to give a gum which on trituration with ether afforded the title compound (0.17 g) as a solid, m.p. 117°–118°.

Analysis Found: C,56.1; H,4.3; N,10.5; $C_{16}H_{16}N_4O.2C_4H_4O_4$ requires C,56.2; H,4.7; N,10.9%.

EXAMPLE 18

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (1.00 g) was suspended in ethanol (40 ml) and concentrated hydrochloric acid (1.00 ml) was added. The mixture was warmed to 40° and charcoal (0.25 g) was added. The resulting suspension was stirred and warmed for 5 min. and then filtered. The filtrate was evaporated in vacuo to ca. 20 ml and was allowed to cool to 20°. Ether (40 ml) was added with stirring over 5 min., and the mixture was stored at 4° overnight. The resulting precipitate was filtered off, washed with ether (2×10 ml), dried in vacuo at room temperature for 2 h

and then at 70° for 7 h to give the title compound (0.95 g), m.p. 288°–291°.

Analysis Found: C,61.4; H,5.8; N,16.7; Cl, 10.7; $C_{17}H_{18}N_4O.HCl$ requires C,61.7; H,5.8; N,16.9; Cl, 10.7%.

EXAMPLE 19

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one sulphate

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (0.81 g) was suspended in absolute ethanol (6 ml) and was warmed at 50° with concentrated sulphuric acid (0.15 ml). More ethanol (4 ml) was added and the mixture was stirred with charcoal (0.1 g). The suspension was then filtered and the collected solid was washed with ethanol (ca. 3 ml). The resulting filtrate was stirred for ca. 1 h at room temperature, tert-butyl methyl ether (10 ml) was added slowly and the mixture was stirred for 20 min. The precipitate was filtered off, washed with ethanol:tert-butyl methyl ether (1:1;6 ml), then with tert-butyl methyl ether (6 ml), and dried in vacuo at 40° for 4 days to give the title compound (0.4 g), m.p. 205°–209°.

Analysis Found: C,49.5; H,5.6; N, 13.5; S,8.4; $C_{17}H_{18}N_4O.\ 1.1H_2SO_4$ requires C,49.9; H,5.4; N, 13.3; S, 8.4%.

EXAMPLE 20

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A suspension of 2,3,4,5-tetrahydro-5-methyl-1H-pyrido[4,3-b]indol-1-one (400 mg) in dry DME (50 ml) was treated with sodium hydride (60% dispersion in oil; 100 mg), and the mixture was stirred at 60° under nitrogen for 6 h. 4-(Chloromethyl)-5-methyl-1-(triphenylmethyl)-1H-imidazole (474 mg) was added and the reaction mixture was stirred at 60° under nitrogen overnight. 2N Hydrochloric acid (10 ml) and water (10 ml) were then added, and the mixture was heated at reflux for 6 h. After cooling, the mixture was basified with 2N sodium hydroxide and the resulting mixture was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (352 mg) as a solid, t.l.c. (System A, 100:8:1) Rf 0.28. ^{1}H-N.m.r.: δ2.2 (3H,s), 3.04 (2H,t), 3.62 (2H,t), 3.72 (3H,s), 4.53 (2H,s), 7.1–7.28 (2H,m), 7.43 (1H,s), 7.47–7.55 (1H,dd), 7.94–8.03 (1H,dd).

EXAMPLE 21

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,5-dihydro-5-methyl-2-[[(5-methyl-1H-imidazol-4-yl)-methyl]-1H-pyrido[4,3-b]indol-1-one (50 mg) and 10% palladium oxide on carbon catalyst (50% aqueous paste; 25 mg) in absolute ethanol (10 ml) was heated at 80° in a hydrogen atmosphere at 80 p.s.i. for 24 h. The suspension was filtered and the filtrate was evaporated to give an oil (49 mg) which was purified by short path column chromatography on silica gel (Merck 7739) eluting with System A (150:10:1) to give the title compound (8 mg) as a solid, t.l.c. (System A, 150:10:1) Rf 0.36. The ^{1}H-n.m.r. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 22

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 2,3,4,5-tetrahydro-2[[5-methyl-1-(triphenylmethyl)-1H-imidazol-4-yl]methyl]-1H-pyrido[4,3-b]indol-1-one (261 mg) in dry DMF (25 ml) was treated with sodium hydride (60% dispersion in oil; 30 mg) and the mixture was stirred at room temperature under nitrogen for 15 min. Iodomethane (0.5M solution in DMF; 2 ml) was then added and stirring was continued for a further 15 min. The reaction mixture was then poured into water (100 ml) and the resulting suspension was extracted with ethyl acetate (2×50 ml). The combined organic extracts were washed with water (2×100 ml), dried and concentrated to give a solid. This was dissolved in a mixture of water (10 ml), THF (10 ml) and glacial acetic acid (10 ml) and heated at reflux for 2 h. After cooling, residual THF was removed in vacuo and the remaining solution was basified (to pH14) by addition of 2N sodium hydroxide. The resulting suspension was extracted with ethyl acetate (2×50 ml) and the combined, dried organic extracts were concentrated onto silica (Merck 7385). FCC eluting with System A (100:8:1) gave the title compound (81 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 23

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (20.0 mg) was dissolved in 98% sulphuric acid (1 ml) and the solution was stirred at 25° for 5 min. The mixture was cautiously poured into 8% aqueous sodium bicarbonate solution (60 ml) and extracted with 10% methanol:dichloromethane (2×60 ml). The combined, dried organic extracts were evaporated in vacuo to leave an oil which was purified by FCC eluting with System A (100:8:1) to give the title compound (13.5 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 24

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl[4-[1,2,3,6-tetrahydro-4-[(2-iodophenyl)methylamino]-6-oxo-1-pyridinyl]methyl]-1H-imidazole-1-sulphonamide (264 mg) in a mixture of dioxane and acetonitrile (2:1; 200 ml) containing triethylamine (2 ml) was irradiated in a pyrex immersion well with a medium pressure 125 W mercury lamp at room temperature for 24 h. The reaction mixture was then concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the title compound (87 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 25

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide (86 mg) in 2N hydrochloric acid (10 ml) and absolute ethanol (2 ml) was heated at 100°–110° for 4 h. The reaction mixture was then cooled and 2N sodium hydroxide (50 ml) was added. The resulting solution was extracted with dichloromethane (2×50 ml) and the combined, dried organic extracts were concentrated onto FCC silica and purified by FCC eluting with System A (100:8:1) to give a solid (36 mg). This was taken up in hot ethyl acetate and purified by slow evaporation to give the title compound (12 mg). The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 26

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of N,N,5-trimethyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-sulphonamide (401 mg) in a mixture of dioxane (150 ml) and acetonitrile (150 ml) containing triethylamine (1 ml) was irradiated at room temperature with a medium pressure mercury lamp for 24 h. The reaction mixture was then concentrated in vacuo onto FCC silica and purified by FCC eluting with System A (100:8:1) to give the title compound (203 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 27

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of phenylmethyl 5-methyl-4-[(2,3,4,5-tetrahydro-5-methyl-1-oxo-1H-pyrido[4,3-b]indol-2-yl)methyl]-1H-imidazole-1-carboxylate (134 mg) in a mixture of absolute ethanol and 2N hydrochloric acid (2:1; 30 ml) was heated on a steam bath for 15 min. After cooling, the solution was concentrated in vacuo to ca. 20 ml and diluted with water (40 ml). The mixture was then washed with ethyl acetate (2×40 ml) and the acidic aqueous layer was basified with potassium carbonate solution. The solution was then extracted with ethyl acetate (3×50 ml) and the combined, dried organic extracts, were concentrated onto FCC silica and purified by FCC eluting with System A (150:8:1) to give a solid. This was dissolved in hot methanol and triturated with ether to give the title compound (69 mg). The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 28

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 2,3,4,5-tetrahydro-2-[[1-(methoxymethyl)-5-methyl-1H-imidazol-4-yl]methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one and 2,3,4,5-tetrahydro-2-[[1-(methoxymethyl)-4-methyl-1H-imidazol-5-yl]methyl]-5-methyl-1H-pyrido[4,3-b]indol-1-one (34 mg) in 49% hydrobromic acid (2 ml) was heated on a steam bath for ca. 3 h. After cooling, the reaction mixture was basified by addition of potassium carbonate solution and extracted with ethyl acetate (3×50 ml). The combined, dried organic extracts were concentrated in vacuo to give the title compound (6 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 29

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 2,3,4,5-tetrahydro-5-methyl-2-[(4-methyloxazol-5-yl)methyl]-1H-pyrido[4,3-b]indol-1-one (100 mg) in formamide (20 ml) was heated at 180° for 24 h. The mixture was then cooled, diluted with water (100 ml) and extracted with dichloromethane (3×100 ml). The combined organic extracts were concentrated in vacuo and the residue was purified by FCC eluting with System A (100:8:1) to give the title compound (40 mg) as a solid. The ^{1}H-n.m.r. and t.l.c. data for this material were consistent with those obtained for the product of Example 20.

EXAMPLE 30

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A solution of 4-[[[(1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (140 mg) in dry dichloromethane (15 ml) was cooled to 5° and the mixture was stirred under nitrogen while phosgene (12% w/w solution in toluene; 1 ml) was added dropwise. The reaction mixture was stirred at room temperature for 2 h, aluminium trichloride (60 mg) was powdered and added, and stirring was continued overnight. After this time methanol (1 ml) was added and the reaction mixture was adsorbed onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the protected derivative of the title compound (42 mg), as a solid, identical (by t.l.c. and m.p.) to the product of Intermediate 27. Deprotection as described in either of Examples 25 or 26 gives the title compound.

EXAMPLE 31

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

A mixture of 4-[[[(3-iodo-1-methyl-1H-indol-2-yl)ethyl]amino]methyl]-N,N,5-trimethyl-1H-imidazole-1-sulphonamide (70 mg), triphenylphosphine (52 mg) and palladium acetate (22 mg) in tri-n-butylamine (5 ml) and dry THF (1 ml) was heated under an atmosphere of carbon monoxide at 120° for 1 h. After cooling the reaction mixture was poured into 2N hydrochloric acid (50 ml) and the resulting mixture was extracted with ethyl acetate (2×50 ml; discarded). The acidic solution was then basified with 2N potassium carbonate and the resulting basic suspension was extracted with ethyl acetate (2×50 ml). The combined, dried organic extracts were concentrated in vacuo to give an oil and residual tri-n-butylamine was removed by distillation to leave a solid. This was adsorbed onto FCC silica and purified by FCC eluting with System A (150:8:1) to give the protected derivative of the title compound (21 mg) as a solid, identical (by t.l.c. and m.p.) to the product of Intermediate 27. Deprotection as described in either of Examples 25 or 26 gives the title compound.

EXAMPLE 32

2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one

5,6-Dihydro-1-[(5-methyl-1H-imidazol-4-yl)methyl]-4-(2-methyl-2-phenylhydrazino)-2(1H)-pyridinone (60 mg) was dissolved in glacial acetic acid (4 ml). Anhydrous zinc chloride (600 mg) was added, and the mixture was heated at 85° for 1.5 h. The cooled mixture was poured into 8% aqueous sodium bicarbonate solution (100 ml) and extracted with ethyl acetate:methanol (10:1) (2×100 ml). The combined, dried organic extracts were evaporated in vacuo to leave a solid which was purified by FCC eluting with System A (100:8:1) to give the title compound (26 mg). The ^{1}H-n.m.r. and t.l.c. data obtained for this material were consistent with those obtained for the product of Example 20.

The following examples illustrate pharmaceutical formulations according to the invention, containing 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-1-yl)methyl]-1H-pyrido[4,3-b]indol-1-one as the active ingredient. Physiologically acceptable salts and/or solvates of this compound, and other compounds of formula (I) and their physiologically acceptable salts and/or solvates may be formulated in a similar manner.

TABLETS FOR ORAL ADMINISTRATION

Tablets may be prepared by the normal methods such as direct compression or wet granulation.

The tablets may be film coated with suitable film forming materials, such as hydroxypropyl methylcellulose, using standard techniques. Alternatively the tablets may be sugar coated.

Direct Compression	
Tablet	mg/tablet
Active Ingredient	0.50
Calcium Hydrogen Phosphate BP*	87.25
Croscarmellose Sodium NF	1.80
Magnesium Stearate BP	0.45
Compression weight	90.00

*of a grade suitable for direct compression.

The active ingredient is passed through a 60 mesh sieve, blended with the calcium hydrogen phosphate, croscarmellose sodium and magnesium stearate. The resultant mix is compressed into tablets using a Manesty F3tablet machine fitted with 5.5 mm, flat bevelled edge punches.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	0.5
Compressible Sugar NF	64.5
Magnesium Stearate BP	0.5
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve, blended with the excipients and compressed using suitable punches. Tablets of other strengths may be prepared by altering either the ratio of active ingredient to excipients or the compression weight and using punches to suit.

Wet Granulation	
Conventional Tablet	mg/tablet
Active Ingredient	0.5
Lactose BP	153.5
Starch BP	30.0
Pregelatinised Maize Starch BP	15.0
Magnesium Stearate BP	1.5
Compression Weight	200.0

The active ingredient is sieved through a suitable sieve and blended with lactose, starch and pregelatinised maize starch. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended with the magnesium stearate. The granules are then compressed into tablets using 7 mm diameter punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to lactose or the compression weight and using punches to suit.

Sub-Lingual Tablet	mg/tablet
Active Ingredient	0.5
Mannitol BP	58.5
Hydroxypropylmethylcellulose	5.0
Magnesium Stearate BP	1.0
Compression Weight	65.0

The active ingredient is sieved through a suitable sieve and blended with the mannitol and hydroxypropylmethylcellulose. Suitable volumes of purified water are added and the powders are granulated. After drying, the granules are screened and blended into tablets using suitable punches.

Tablets of other strengths may be prepared by altering the ratio of active ingredient to mannitol or the compression weight and punches to suit.

tablet	mg/tablet
Active Ingredient	0.5
*Starch 1500	98.5
Magnesium Stearate BP	1.0
Fill Weight	100.0

*a form of directly compressible starch.

The active ingredient is sieved and blended with the excipients. The mix is filled into size No. 2 hard gelatin capsules using suitabled machinery. Other doses may be prepared by altering the fill weight an if necessary changing the capsule size to suit.

SYRUP

This may be either a sucrose or sucrose free presentation.

A. Sucrose Syrup		mg/5 ml dose
Active Ingredient		0.5
Sucrose BP		2750.0
Glycerine BP		500.0
Buffer, Flavour, Colour, Preservative		as required
Purified Water BP	to	5.0 ml

The active ingredient, buffer, flavour, colour and preservative are dissolved in some of the water and the glycerine is added. The remainder of the water is heated to dissolve the sucrose and is then cooled. The two solutions are combined, adjusted to volume and mixed. The syrup is clarified by filtration.

B. Sucrose-Free		mg/5 ml dose
Active Ingredient		0.5
Hydroxypropylmethylcellulose USP (viscosity type 4000)		22.5
Buffer, Flavour, Colour, Preservative, Sweetener		as required
Purified Water BP	to	5.0 ml

The hydroxypropylmethylcellulose is dispersed in hot water, cooled and then mixed with an aqueous solution containing the active ingredient and the other components of the formulation. The resultant solution is adjusted to volume and mixed. The syrup is clarified by filtration.

INJECTION FOR INTRAVENOUS ADMINISTRATION		
	mg/ml	
Active Ingredient	0.05	0.5
Sodium Chloride BP	as required	as required
Water for Injection BP to	1.0 ml	1.0 ml

Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted, using acid or alkali, to that of optimum stability and/or facilitate solution of the active ingredient. Alternatively, suitable buffer salts may be used.

The solution is prepared, clarified and filled into appropriate size ampoules sealed by fusion of the glass. The injection is sterilised by heating in an autoclave using one of the acceptable cycles. Alternatively, the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions. The solution may be packed under an inert atmosphere of nitrogen or other suitable gas.

METERED DOSE PRESSURISED AEROSOL		
Suspension Aerosol	mg/metered dose	Per can
Active Ingredient micronised	0.050	12.0 mg
Oleic Acid BP	0.020	4.80 mg
Trichlorofluoromethane BP	23.64	5.67 g
Dichlorodifluoromethane BP	61.25	14.70 g

The active ingredient is micronised in a fluid energy mill to a fine particle size range. The oleic acid is mixed with the trichlorofluoromethane at a temperature of 10°–15° C. and the micronised drug is mixed into the solution with a high shear mixer. The suspension is metered into aluminium aerosol cans and suitable metering valves, delivering 85 mg of suspension are crimped onto the cans and the dichlorodifluoromethane is pressure filled into the cans through the valves.

	Solution Aerosol	
	mg/metered dose	Per can
Active Ingredient	0.05	12.0 mg
Ethanol BP	7.500	1.80 g
Trichlorofluoromethane BP	18.875	4.53 g
Dichlorodifluoromethane BP	48.525	11.65 g

Oleic acid BP, on a suitable surfactant e.g. Span 85 (sorbitan trioleate) may also be included).

The active ingredient is dissolved in the ethanol together with the oleic acid or surfactant if used. The alcoholic solution is metered into suitable aerosol containers followed by the trichlorofluoromethane. Suitable metering valves are crimped onto the containers and dichlorodifluoromethane is pressure filled into them through the valves.

Inhalation Cartridges		
		mg/cartridge
Active Ingredient (micronised)		0.05
Lactose BP	to	25.00

The active ingredient is micronised in a fluid energy mill to a fine particle size range prior to blending with normal tabletting grade lactose in a high energy mixer. The powder blend is filled into No. 3 hard gelatin capsules on a suitable encapsulating machine. The contents of the cartridges are administered using a powder inhaler.

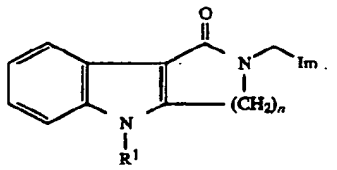
SUPPOSITORY	
Active Ingredient	0.5 mg
*Witepsol H15 to	1.0 g

*Witepsol H15 is a proprietary grade of Adeps Solidus Ph. Eur.

A suspension of the active ingredient is prepared in the molten Witepsol and filled, using suitable machinery, into 1g size suppository moulds.

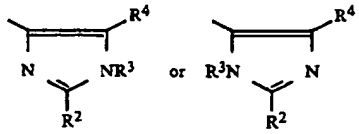
We claim:

1. A compound of formula (I)



(I)

wherein Im represents an imidazolyl group of the formula:



and R^1 represents a hydrogen atom or a group selected from C_{1-6}alkyl, C_{3-6}alkenyl, C_{3-10}alkynyl, C_{3-7}cycloalkyl, C_{3-7}cycloalkyl C_{1-4}alkyl, phenyl, phenylC_{1-3}alkyl, phenylmethoxymethyl, phenoxyethyl phenoxymethyl;

one of the groups represented by R^2, R^3 and R^4 is a hydrogen atom or a C_{1-6}alkyl, C_{3-7}cycloalkyl, C_{3-6}alkenyl, phenyl or phenylC_{1-3}alkyl group, and

each of the other two groups, which may be the same or different, represents a hydrogen atom or a C_{1-6}alkyl group;

n represents 2 or 3;

or a physiologically acceptable salt or solvate thereof.

2. A compound according to claim 1 in which R^1 represents a C_{1-4}alkyl, C_{3-4}alkynyl, C_{5-6}cycloaklyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, or phenylmethoxymethyl.

3. A compound according to claim 1 in which R^2, R^3 and R^4 each independently represent a hydrogen atom or a C_{1-3}alkyl group.

4. A compound according to claim 1 in which R^1 represents a hydrogen atom or a C_{1-4}alkyl, C_{3-4}alkenyl, C_{3-4}alkynyl, C_{5-6}cycloaklyl, C_{5-6}cycloalkylmethyl, phenylC_{1-2}alkyl, or phenylmethoxymethyl, R^2 represents a hydrogen atom; and R^3 and R^4 each represent a hydrogen atom or a C_{1-3}alkyl group.

5. A compound according to claim 1 in which R^1 represents a methyl, n-propyl, prop-2-ynyl, cyclopentyl, cyclopentylmethyl, or benzyl; R^2 and R^3 each represent a hydrogen atom; and R^4 represents a methyl group.

6. A compound according to claim 4 in which n represents 2.

7. A compound according to claim 5 in which n represents 2.

8. 2,3,4,5-Tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one; or a physiologically acceptable salt or solvate thereof.

9. A compound selected from:

2,3,4,5-Tetrahydro-5-(phenylmethyl)-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;

5-cyclopentyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one;

2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-5-propyl-1H-pyrido[4,3-b]indol-1-one;

5-(cyclopentylmethyl)-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1one;

3,4,5,6-tetrahydro-6-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-azepino[4,3-b]indol-1(2H)-one;

2,3,4,5-tetrahydro-N,N-dimethyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1-oxo-5H-pyrido[4,3-b]indole-5-carboxamide;

2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl-5-(2-propynyl)-1H-pyrido[4,3-b]indol-1-one;

or a physiologically acceptable salt and solvate thereof.

10. A compound according to claim 1 in the form of a hydrochloride, hydrobromide, sulphate, alkylsulphonate, arylsulphonate, phosphate, acetate, citrate, succinate, tartrate, fumarate or maleate salt.

11. The compound of claim 8 in the form of a hydrochloride salt.

12. The compound of claim 8 in the form of a maleate salt.

13. A pharmaceutical composition which comprises an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof together with at least one physiologically acceptable carrier or excipient.

14. A pharmaceutical composition according to claim 13 in a form adapted for oral or parenteral administration.

15. A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5- tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

16. A pharmaceutical composition according to claim 13 wherein the active ingredient is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1H-pyrido[4,3-b]indol-1-one hydrochloride.

17. A method of treating a condition which is ameliorated by antagonism of $5HT_3$ receptors which comprises administering to a patient an effective amount of a compound of formula (I) as defined in claim 1 or a physiologically acceptable salt or solvate thereof to relieve said condition.

18. A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

19. A method according to claim 17 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

20. A method according to claim 17 wherein the condition which is ameliorated by antagonism of $5HT_3$ receptors is anxiety.

21. A method according to claim 20 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

22. A method according to claim 20 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

23. A method according to claim 17 wherein the condition which is ameliorated by antagonism of $5HT_3$ receptors is schizophrenia.

24. A method according to claim 23 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

25. A method according to claim 23 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

26. A compound according to claim 1 which is 5-ethyl-2,3,4,5-tetrahydro-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

27. A method according to claim 17 for the treatment of irritable bowel syndrome.

28. A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

29. A method according to claim 27 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

30. A method according to claim 17 wherein the condition which is ameliorated by antagonism of $5HT_3$ receptors is dyspepsia.

31. A method according to claim 30 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

32. A method according to claim 30 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

33. A method according to claim 17 wherein the condition which is ameliorated by antagonism of 5-HT_3 receptors is reflux oesophagitis.

34. A method according to claim 33 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one or a physiologically acceptable salt or solvate thereof.

35. A method according to claim 33 wherein the compound of formula (I) is 2,3,4,5-tetrahydro-5-methyl-2[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one hydrochloride.

* * * * *

EXHIBIT 6

Terminal Disclaimer filed in United States

Patent Application No. 07/741,570

U.S. Patent No. 5,360,800

Express Mail Label
No. EM484297842US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	)	
IAN H COATES et al	)	
Serial Number: 07/741,570	)	**Group Art Unit: 1203**
Filed: August 7, 1991	)	**Examiner: Alan L Rotman**
For: LACTAM DERIVATIVES	)	

TERMINAL DISCLAIMER

Honorable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

Your Petitioner, **Glaxo Group Limited** (henceforth referred to as "Assignee"), having a place of business at **Glaxo House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, England,** represents that it is the owner by assignment of the entire right and title to the above-captioned patent application and the invention and improvements therein disclosed for the United States by virtue of an assignment from the inventors, dated **August 22, 1988** and recorded at **Reel 4993, Frames 723-725**, on **September 15, 1988**.

Assignee, who is also owner of the entire right and title to U.S. patent Number **5,183,820** by assignment recorded at **Reel 5773, Frames 178-180** on **July 17, 1991,** hereby disclaims the terminal part of any patent granted on the above-captioned application which would extend beyond the expiration date of the full statutory term as presently shortened by any terminal disclaimer of U.S. Patent Number **5,183,820**, and hereby agrees that any patent so granted on the above-captioned application shall be enforceable only for and during such period that the legal title to said patent shall be the same as the legal title to U.S. Patent Number **5,183,820,** this agreement to run with any patent granted on the above-captioned application and to be binding upon the grantee, its successors or assigns. Notwithstanding the above disclaimer, Assignee does not waive any rights available under the provisions of 35 U.S.C. §§ 155 and 156.

Assignee does not disclaim any terminal part of any patent granted on the above-captioned application prior to the expiration date of the full statutory term as present shortened by any terminal disclaimer of U.S. Patent Number **5,183,820** in the event that it later expires for failure to pay a maintenance fee, is held unenforceable, is found invalid, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. § 1.321(a), has all claims cancelled by a re-examination certificate, or is otherwise terminated prior to the expiration of its statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above. Assignee does not disclaim any terminal part of any patent granted on the above-captioned application resulting from any extension of that patent granted under the provisions of 35 U.S.C. §§ 155, 155(a) and 156.

Documentary evidence which establishes a chain of title of the above-captioned U.S. patent application from the original owner to the Assignee has been reviewed by Assignee and Assignee certifies under 37 C.F.R. §3.73(b) that to the best of Assignee's knowledge and belief, title is in the assignee seeking to take the present action.

I, Alan Hesketh, am empowered to act on behalf of the Assignee, and I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statement and the like so made are punishable by fine, or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the above-captioned application.

Signed at Greenford, Middlesex, England

this 24th **day of** February **1994.**

GLAXO GROUP LIMITED
by their Attorney

Alan Hesketh

EXHIBIT 7

Assignment to Glaxo Group Limited of Application for Letters Patent of United States Patent Application No. 07/691,814

U.S. Patent No. 5,183,820

Express Mail Label No. EM484297842US

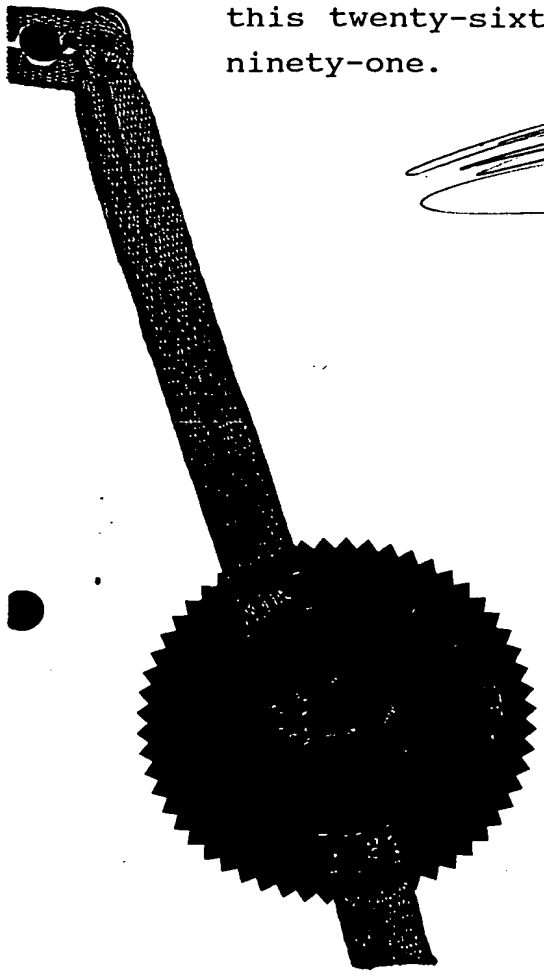
SN359 USA

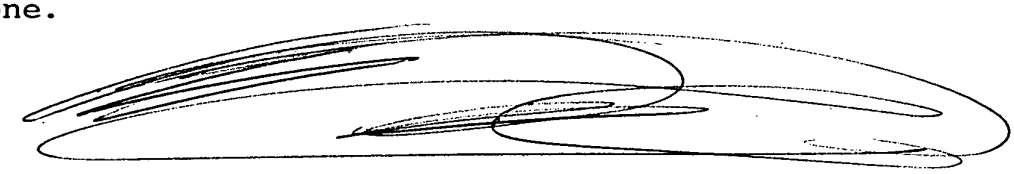
I, **RICHARD GRAHAM ROSSER**, of the City of London, Notary Public duly admitted and sworn practising in the said City,

DO HEREBY CERTIFY AND ATTEST:

THAT the signatures set and subscribed at foot of the hereunto annexed document are genuine, the same having been duly subscribed thereto by **IAN HAROLD COATES, ALEXANDER WILLIAM OXFORD, PETER CHARLES NORTH** and **BARRY JOHN PRICE**, whose identities I attest.

IN TESTIMONY WHEREOF I have hereunto set my hand and affixed my Seal of Office in the City of London aforesaid, this twenty-sixth day of June One thousand nine hundred and ninety-one.





REEL 5773 FRAME 178

APOSTILLE

(Hague Convention of 5 October 1961/Convention de La Haye du 5 octobre 1961)

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document/Le présent acte public

2. has been signed by
a été signé par R.G. ROSSER

3. acting in the capacity of
agissant en qualité de Notary Public

4. bears the seal/stamp of
est revêtu du sceau/timbre de THE SAID NOTARY PUBLIC

Certified/Attesté

5. at London/à Londres

6. the/le 27 JUN 1991

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs/
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/sous No G 080288

9. Stamp:
timbre:

FOREIGN AND COMMONWEALTH OFFICE
LONDON

10. Signature:

B KAHLOW

For the Secretary of State/Pour le Secrétaire d'Etat

REEL 5773 FRAME 179

ASSIGNMENT

For good and valuable considerations, the receipt and sufficiency of which is hereby acknowledged, WE

Ian Harold COATES
Alexander William OXFORD
Peter Charles NORTH
Barry John PRICE

do hereby sell, assign, convey and set over to our assignees,

Glaxo Group Limited, a British company,
of Clarges House, 6/12 Clarges Street,
London, W1Y 8DH, England.

our entire right, title and interest in and to an invention entitled

Lactam Derivatives

and in and to the application for Letters Patent of the United States thereon, filed 26th April, 1991 as Application Serial No. 07/691,814, to any patent or patents that may issue on said application and invention in the United States of America and foreign countries, to assist in securing which we hereby covenant and agree on behalf of ourselves, our heirs, executors and legal representatives, to execute without further compensation all papers and assignment connected with such patent or application therefor and I do hereby authorise and request the Commissioner of Patents to issue any patents maturing on said US application to our assignee as the beneficial owner thereof;

IN WITNESS WHEREOF, We have hereunto set our hand and seal this 24th day of June 1991

Ian Harold Coates
Ian Harold COATES

Alexander William Oxford
Alexander William OXFORD

Peter Charles North
Peter Charles NORTH

Barry John Price
Barry John PRICE

EXHIBIT 8

Maintenance Fee Statement for

U.S. Patent No. 5,360,800

Express Mail Label No. EM484297842US

OP 156911

THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:
UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

October 04, 1999

THIS IS TO CERTIFY THAT ANNEXED IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

MAINTENANCE FEE STATEMENT
SERIAL NUMBER: 07/741,570
FILING DATE: August 07, 1991

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

T. WALLACE
Certifying Officer

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
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2900 Crystal Drive
Arlington, VA 22202-3513

DATE MAILED
09/30/1999

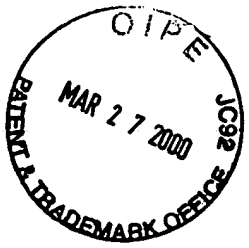
RICHARD E. FICHTER
BACON AND THOMAS
PTO BOX 76
ARLINGTON VA 22202

In response to your communication of 09/30/1999 concerning the status of payment of maintenance fees due, the following is provided:

Patent Number : 5360800
Application Serial Number : 07/741,570
Application Filing Date : 08/07/1991
Issue Date : 11/01/1994
Status: 8TH YEAR FEE WINDOW OPENS: 11/01/2001

(PTOL-438)

part of # 20



EXHIBITS 9A – 9G

Document Chronology / Due Diligence Logs for IND No. 34,672,

Document Chronology / Due Diligence Logs for IND No. 39,083,

Document Chronology / Due Diligence Logs for IND No. 45,128,

Transcript of Dr. Camilleri's remarks before the Gastrointestinal Drugs Advisory Committee

Document Chronology / Due Diligence Logs for IND No. 48,487,

Document Chronology / Due Diligence Logs for NDA 21-107, and

Document Chronology / Due Diligence Logs for IND No. 59,496

Express Mail Label No. EM484297842US

EXHIBIT 9A

Document Chronology / Due Diligence Logs for

IND No. 34,672,

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
1	10-APR-90	LETTER from GLAXO to FDA	ORIGINAL APPLICATION	BIOAVAILABLTY/PHARMACOKINETICS	1.001-	000
			ORIGINAL APPLICATION	PROTOCOL	1.010	
			ORIGINAL APPLICATION	DOSING REGIMEN		
			ORIGINAL APPLICATION	SAFETY		
			ORIGINAL APPLICATION	NON-CLINICAL GENERAL		
			ORIGINAL APPLICATION	PHARMACOLOGY		
			ORIGINAL APPLICATION	TOXICOLOGY		

GR68755 IS A POTENT, SELECTIVE COMPETITIVE ANTAGONIST AT THE 5-HT3 RECEPTOR SITE. FUTURE STUDIES IN AGE ASSOCIATED MEMORY IMPAIRMENT (AAMI) ARE PLANNED.

PROTOCOL	INV#	INVESTIGATOR
S3B-101	2267	Kisicki James C.

2	11-APR-90	MEMO from GLAXO to GLAXO	INTERNAL COMMUNICATION	FDA REVIEW STATUS		
			INTERNAL COMMUNICATION	UPDATE		

IND DELIVERED 10-APR-90| IND # ASSIGNED 34672| 30 WAITING PERIOD BEFORE CLINICAL TRIALS MAY BEGIN WILL BE UP 10-MAY-90|

3	17-APR-90	LETTER from FDA to GLAXO	ACKNOWLEDGEMENT	UPDATE	2.001-	
					2.001	

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 34672	1	000	LETTER from GLAXO to FDA	10-APR-90

4	29-JUN-90	LETTER from FDA to GLAXO	REQUESTS/COMMENTS	C M C INCLUSIVE/GENERAL	2.001-	
			REQUESTS/COMMENTS	CLINICAL INCLUSIVE/GENERAL	2.001	
			REQUESTS/COMMENTS	PROTOCOL		
			REQUESTS/COMMENTS	INVESTIGATIONAL DRUG LABELING		

FDA REQUESTS ADDITIONAL CMC INFORMATION & SUGGESTS STUDY S3B-101 INCLUDE MORE FREQUENT VITAL SIGNS MONITORING. ALSO CONFIRMS 5.10.90 VERBAL ACCEPTANCE TO INITITATE CLINICAL STUDY.

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		REFERENCE APPLICATION: IND 34672	REFERENCE ACT#: 1	SUP#/ SER#: 000	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 10-APR-90
		PROTOCOL: S3B-101	INV#:	INVESTIGATOR:		
5	25-JUL-90/ 24-JUL-90	TELECON from FDA to GLAXO	TELECONFERENCE TELECONFERENCE RESPONSE	FDA REVIEW STATUS FDA CONSULT/GUIDANCE C M C INCLUSIVE/GENERAL	2.001- 2.001	
		RESPONDING TO GLX REQUEST OF 7.11.90, CSO DECORTE INDICATES CHEMISTRY QUESTIONS OF 6.29.90 WERE SENT IN ERROR & INSTRUCTED GLX NOT TO RESPOND TO QUESTIONS 6,8,9,10,11. GLX INDICATES RESPONSE TO REMAINING QUESTIONS FORTHCOMING.				
		REFERENCE APPLICATION: IND 34672	REFERENCE ACT#: 4	SUP#/ SER#:	METHOD OF COMMUNICATION: LETTER from FDA to GLAXO	DOC/ACT DATE: 29-JUN-90
6	15-NOV-90	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CLINICAL INFO AMND: CLINICAL INFO AMND: CLINICAL SPONSOR COMMITMENT	DP: CONTAINER/CLOSURE SYSTEM DP: METHOD OF MANUFACTURER DP: SPECS/ANALYTICAL METHODS DP: STABILITY DS: SPECS/ANALYTICAL METHODS DS: STABILITY DP: FORMULATION PROTOCOL FOREIGN INFORMATION STUDY REPORT CLINICAL INCLUSIVE/GENERAL	2.001- 2.001	001
		RESPONDING TO 6.29.90 LTR, GLX SUBMITS CMC INFORMATION INCLUDING ADDITIONAL TABLET STRENGTH (2MG) & UPDATED D-S STABILITY DATA & ADDITIONAL IDENTITY SPECIFICATION FOR D-S. ADDITIONALLY GLX WITHDRAWS 1MG TABLET STRENGTH. GLX ALSO COMMENTS ON AGENCY REQUEST FOR INCREASED VITAL SIGN MONITORING & CATALOGS CV PARAMETERS TO BE MEASURED DURING NEXT VOLUNTEER PROTOCOL. GLX SUMMARIZES UK SAFETY & TOLERANCE STUDIES FOR FDA & SUBMITS RECHALLENGE STUDY REPORT.			

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 34672	4		LETTER from FDA to GLAXO	29-JUN-90
IND 34672	5		TELECON from FDA to GLAXO	25-JUL-90/ 24-JUL-90

PROTOCOL	INV#	INVESTIGATOR
GHP8923		
GHP8938		
GHP9005		
S3B-101		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
7	17-JAN-91	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	FOREIGN INFORMATION	3.001-	002
			INFO AMND: CLINICAL	STUDY REPORT	3.005	
			PRTCL AMND: NEW PROTOCOL	PROTOCOL		
			PRTCL AMND: NEW PROTOCOL	PRIN-INVESTIGATOR ADD		
			INFO AMND: PHARM/TOXICOLOGY	STUDY REPORT		
			INFO AMND: PHARM/TOXICOLOGY	TOX: MUTAGENICITY		
			INFO AMND: PHARM/TOXICOLOGY	ADME		

NEW PROTOCOL S3B-102 (TOLERANCE/VOLUNTEERS) SUBMITTED. CLINICAL DATA TO SUPPORT PROTOCOL INCLUDES: STUDY REPORT GPK/90/006 (PHARMACOKINETIC/YOUNG & ELDERLY/ORAL VS IV), SUMMARY REPORT FOR S3B-101 (ASCENDING-DOSE, SAFETY & PHARMACOKINETICS/VOLUNTEERS), GPK/90/008 REPORT (PHARMACOKINETCIS/TOLERANCE/4MG BID X 9-1/2DAYS/VOLUNTEERS). NONCLINICAL REPORTS ALSO INCLUDED AS FINAL REPORTS.

PROTOCOL	INV#	INVESTIGATOR
S3B-101		
S3B-102	2548	Hunt Thomas L.
S3B-102		

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
8	28-FEB-91	LETTER from GLAXO to FDA	PRTCL AMND: PROTOCOL CHANGE	PROTOCOL	4.001- 4.001	003

PROTOCOL MODIFICATION TO COLLECT HOLTER MONITOR RECORD DURING SCREEN PERIOD BEFORE DAY 1 (BASAELINE).

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		PROTOCOL S3A-102 INV#	INVESTIGATOR			
9	28-MAR-91	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	4.001-4.001	004
		MFG CONTROL# CGS01977	ADR PROCESS 10-DAY WRITTEN ISR	REPORT CODE I	SUBMISSION DATE 28-MAR-91	
10	04-APR-91/ 03-APR-91	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL	4.001-4.001	

RMO CRANDALL CONTACTS GLX TO DETERMINE STATUS OF S3B-102 STUDY. GLX REPLIES STUDY COMPLETED, DATA ANALYSIS PENDING.

		PROTOCOL S3B-102 INV#	INVESTIGATOR			
11	02-MAY-91	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY	C M C INCLUSIVE/GENERAL	4.001-4.001	005
			RESPONSE	C M C INCLUSIVE/GENERAL		

AS COMMITTED IN 11.15.90 RESPONSE TO FDA 6.29.90 LTR, GLX PROVIDES REVISED METHODOLOGY & DATA FOR IMPURITIES & RESIDUAL SOLVENT DETERMINATIONS. SPECIFICALLY, 1)HPTLC USED TO CHARACTERIZE IMPURITIES, WILL ALSO SUPPORT SUITABILITY OF HPLC METHODOLOGY FOR ROUTINE ANALYSIS; 2)CHROMATOGRAPHS FOR UNDEGRADED & DEGRADED SAMPLES; 3)GC METHOD TO REPLACE NMR TO DETERMINE RESIDUAL SOLVENT IN D-S; 4)REVISED D-S SPECIFICATION FOR SOLVENT LEVEL.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 34672	4		LETTER from FDA to GLAXO	29-JUN-90
IND 34672	6	001	LETTER from GLAXO to FDA	15-NOV-90

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
12	22-MAY-91	LETTER from GLAXO to FDA	ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE CLINICAL DEVEL PROGRAM PROTOCOL CLINICAL STUDY STATUS SAFETY NON-CLINICAL GENERAL	4.001- 4.001	006
		REPORT PERIOD COVERS APRIL 1990 TO APRIL 1991.				
13	02-JUL-91	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY	SAFETY STUDY REPORT	4.001- 4.001	007
		GLX SUMMARIZES FINDINGS RELATED TO PRECLINICAL SAFETY STUDIES W/COMPOUND, SPECIFICALLY POSITIVE AMES TEST FOR GR68755C INTERMEDIATE.				
		PROTOCOL INV# INVESTIGATOR WPT/90/261 WPT/90/304				
14	01-AUG-91/ 31-JUL-91	TELECON from FDA to GLAXO	HOLD ON IND (ENTIRE DRUG PRG)	UPDATE	4.001- 4.001	
		CSO DeCORTE CALLS TO INFORM GLX THAT FDA WAS PLACING A CLN HOLD ON GR68755 AS A RESULT OF THE POSITIVE AMES TEST RPT.				
		REFERENCE APPLICATION: IND 34672 · REFERENCE ACT#: 13 · SUP#/SER#: 007 · METHOD OF COMMUNICATION: LETTER from GLAXO to FDA · DOC/ACT DATE: 02-JUL-91				
15	01-NOV-91	LETTER from FDA to GLAXO	GENERAL CORRESPONDENCE	FDA CONSULT/GUIDANCE	4.001- 4.001	
		FDA LTR ADDRESSES ISSUES AFFECTING IMPLEMENTATION OF THE "CLINICAN'S GLOBAL ASSESSMENT", ONE OF THE TWO OUTCOME MEASURES THAT THE FDA HAS IDENTIFIED AS ESSENTIAL TO THE ASSESSMENT OF THE EFFICACY OF ANTIDEMENTIA DRUG PRODUCTS IN CONTROLLED CLINICAL TRIALS.				

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
16	04-DEC-91	LETTER from GLAXO to FDA	FOLLOWUP TO WRITTEN ADR/ISR	SAFETY	4.001- 4.001	008

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
CGS01977	FOLLOWUP TO WRITTEN ADR/ISR	F	04-DEC-91

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
17	18-DEC-91	LETTER from GLAXO to FDA	INFO AMND: CLINICAL INFO AMND: CLINICAL	UPDATE STUDY REPORT	4.001- 4.001	009

AMEND TO PROVIDE AMENDMENT TO RPT GMH/89/024 WHICH DOCUMENT THE DISCREPANCY OF ONE SUBJECT WITH TWO DIFFERENT REFERENCE NUMBERS.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
18	10-FEB-92	LETTER from GLAXO to FDA	ANIMAL ADR INFO AMND: PHARM/TOXICOLOGY	SAFETY SAFETY	5.001- 5.006	010

SUBMIT FOLLOW-UP INFO TO SAFETY REPORT SUBMITTED 02-JUL-91. SAFETY RPT EMERGED IN PRECLN SAFETY STUDIES WITH GR68755C.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
19	19-FEB-92	LETTER from GLAXO to FDA	INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY INFO AMND: CMC/MICROBIOLOGY	DP: METHOD OF MANUFACTURER DP: SPECS/ANALYTICAL METHODS DP: STABILITY DP: FORMULATION	6.001- 6.001	011

AMEND TO PROVIDE UPDATED CMC INFO. DESCRIBE NEW MFG PROCESS, REVISED SPECS & ANALYTICAL METHODS. UPDATED STABILITY DATA ON PREVIOUS FORMULATION & NEW 1mg TABLET FORMULATION. INTRODUCE NEW TABLET FORMULATION FOR USE IN CLN STUDIES, INTENDED TO REPLACE THE PREVIOUS 1mg TABLET GRANULATION FORMULATION.

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
20	29-APR-92/ 28-APR-92	TELECON from FDA to GLAXO	TELECONFERENCE TELECONFERENCE	MEETING INFO/DETAILS NON-CLINICAL GENERAL	6.001- 6.001	

CSO NIGHSWANDER CALLS TO SCHEDULE TELECONFERENCE FOR 11-MAY-92 TO DISCUSS FDA PRECLN CONCERN WITH COMPOUND FOR INDICATION OF AGE ASSOCIATED MEMORY IMPAIRMENT (AAMI). FDA WILL ALSO

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		EXPLAIN APPARENT INCONSISTENCY W/THIS COMPOUND IN HANDLING OF THE 2 INDs. IND 34,672 (AAMI) ON CLN HOLD & IND 39,083 (SCHIZOPHRENIA) IS NOT.				
21	30-APR-92	LETTER from GLAXO to FDA	ANNUAL REPORT (IND)	UPDATE	6.001-	012
			ANNUAL REPORT (IND)	DP: METHOD OF MANUFACTURER	6.001	
			ANNUAL REPORT (IND)	DP: SPECS/ANALYTICAL METHODS		
			ANNUAL REPORT (IND)	DP: FORMULATION		
			ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE		
			ANNUAL REPORT (IND)	CLINICAL STUDY STATUS		
			ANNUAL REPORT (IND)	SAFETY		
			ANNUAL REPORT (IND)	NON-CLINICAL GENERAL		
		COVERING PERIOD APRIL, 91 TO APRIL, 92.				
22	12-MAY-92/ 11-MAY-92	TELECON from GLAXO to FDA	TELECONFERENCE	NON-CLINICAL GENERAL	6.001- 6.001	
		ON 11-MAY-92 A TELECONFERENCE WAS HELD TO DISCUSS PRECLINICAL ISSUES WITH FDA.				
23	07-JUL-92	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY	TOXICOLOGY	6.001-	013
			RESPONSE	TOXICOLOGY	6.001	
		GLX PROVIDES ADDITIONAL PHARMACOLOGY/TOXICOLOGY INFORMATION IN RESPONSE TO FDA REQUEST. (WPT/91/409)				

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 34672	22		TELECON from GLAXO to FDA	12-MAY-92/ 11-MAY-92

24	06-OCT-92	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY	NON-CLINICAL GENERAL	7.001-	014
			INFO AMND: PHARM/TOXICOLOGY	TOXICOLOGY	7.001	
		SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF THE EFFECT OF GR68755 ON HEARING PERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR RATS & A 12 MONTH ORAL STUDY IN BEAGLE DOGS.				

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
25	04-JUN-93	LETTER from GLAXO to FDA	ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND) ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE CLINICAL STUDY STATUS SAFETY NON-CLINICAL GENERAL	7.001- 7.001	015
		COVERING ANNUAL REPORTING PERIOD.				
26	03-DEC-93	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	7.001- 7.001	016

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0002909	10-DAY WRITTEN ISR	I	03-DEC-93

27	24-JAN-94	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY	7.001- 7.001	017

MFG CONTROL#	ADR PROCESS	REPORT CODE	SUBMISSION DATE
B0003499	10-DAY WRITTEN ISR	I	24-JAN-94

28	18-FEB-94	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	STUDY REPORT	8.001- 8.004	018
		PROVIDE FINAL CLINICAL STUDY REPORT UCP/92/019 (PROTOCOL S3A-102).				

PROTOCOL	INV#	INVESTIGATOR
S3A-102		

29	25-MAR-94	LETTER from GLAXO to FDA	10-DAY WRITTEN ISR	SAFETY		019

Application: IND 34672 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
			MFG CONTROL# B0004015 ADR PROCESS 10-DAY WRITTEN ISR	REPORT CODE I SUBMISSION DATE 25-MAR-94		
30	09-JUN-94	LETTER from GLAXO to FDA	ANNUAL REPORT (IND) ANNUAL REPORT (IND) INACTIVATES IND	SAFETY NON-CLINICAL GENERAL UPDATE		020
		SUBMIT ANNUAL REPORT SUMARIZING PROGRESS OF INVESTIGATIONS DURING THE INTERVAL APRIL, 93 THROUGH APRIL, 94. ALSO SUBMIT RQST FOR THIS IND TO BE PUT ON INACTIVE STATUS AS NO PATIENTS HAVE BEEN ENTERED INTO CLN TRIALS SINCE 30-JUL-91 AND AT THIS TIME GLX HAS NO PLANS FOR ADDTL DEVELOPMENT ACTIVITY OF THIS COMPOUND.				
		REFERENCE APPLICATION: IND 39083	REFERENCE ACT#: 17	SUP#/ SER#: 008	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 08-JUN-94
31	22-JUL-94	LETTER from FDA to GLAXO	INACTIVATES IND	ADMINISTRATIVE		
		IND PLACED ON INACTIVE STATUS				

Application: IND 34672; GR68755C (alosetron) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Apr-1990	Glaxo Wellcome Correspondence 34672	Initial Investigational New Drug Application		0000
09-Jun-1994	Glaxo Wellcome Correspondence 34672	Request to Inactivate IND		0020
22-Jul-1994	Food and Drug Administration Correspondence IND 34,672; GR68755C (alosetron) Tablets Acknowledgement	Acknowledgement	Other	

EXHIBIT 9B

Document Chronology / Due Diligence Logs for

IND No. 39,083,

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
1	11-MAR-92	LETTER from GLAXO to FDA	INCORPORATION BY REFERENCE	C M C INCLUSIVE/GENERAL	1.001-	000
			ORIGINAL APPLICATION	C M C INCLUSIVE/GENERAL	1.011	
			ORIGINAL APPLICATION	INVESTIGATOR BROCHURE		
			ORIGINAL APPLICATION	CLINICAL DEVEL PROGRAM		
			ORIGINAL APPLICATION	PROTOCOL		
			ORIGINAL APPLICATION	PRIN-INVESTIGATOR ADD		
			ORIGINAL APPLICATION	PATIENT POPULATION		
			ORIGINAL APPLICATION	STUDY REPORT		
			ORIGINAL APPLICATION	MONITOR		
			ORIGINAL APPLICATION	PHARMACOLOGY		
			ORIGINAL APPLICATION	TOXICOLOGY		
			ORIGINAL APPLICATION	TOX: REPRO/TERATOGENICITY		
			ORIGINAL APPLICATION	TOX: MUTAGENICITY		
			ORIGINAL APPLICATION	ADME		

SUBMIT NEW IND TO CONDUCT CLN STUDIES IN SCHIZOPHRENIA. ALSO SUBMIT MOST RECENT SUBMISSION OF CMC DATA TO IND 34,672 WHICH INCLUDES FORMULATION INFO FOR CLN SUPPLIES TO BE USED IN CLN STUDY PROPOSED IN THIS IND. NOTE STUDY MONITOR AS POLLY SANDERSON, Ph.D AND JOE DeVEAUGH-GEISS, M.D. AS SAFETY MONITOR.

REFERENCE APPLICATION	REFERENCE ACT#	SUP#/ SER#	METHOD OF COMMUNICATION	DOC/ACT DATE
IND 34672	1	000	LETTER from GLAXO to FDA	10-APR-90

PROTOCOL	INV#	INVESTIGATOR
S3B-201	4666	Meltzer Herbert
S3B-201	4825	Marder Stephen
S3B-201	4826	Miller Marvin J.
S3B-201		

3	13-MAR-92	MEMO from GLAXO to GLAXO	INTERNAL COMMUNICATION	UPDATE		

SCHIZOPHRENIA IND DELIVERED TO FDA & IND NUMBER ASSIGNED.

2	16-MAR-92	LETTER from FDA to GLAXO	ACKNOWLEDGEMENT	UPDATE		

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		RECEIPT OF NEW IND ACKNOWLEDGED, IND # ASSIGNED, DATE OF RECEIPT NOTED AS 12-MAR-92.				
		REFERENCE APPLICATION: IND 39083 / REFERENCE ACT#: 1 / SUP#/SER#: 000 / METHOD OF COMMUNICATION: LETTER from GLAXO to FDA / DOC/ACT DATE: 11-MAR-92				
4	13-APR-92/ 09-APR-92	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	FDA REVIEW STATUS		
		CSO HIGGINS CALLS TO COMMUNICATE FDA's DECISION ON RVW OF NEW IND IN TREATMENT OF SCHIZOPHRENIA.				
		REFERENCE APPLICATION: IND 39083 / REFERENCE ACT#: 1 / SUP#/SER#: 000 / METHOD OF COMMUNICATION: LETTER from GLAXO to FDA / DOC/ACT DATE: 11-MAR-92				
5	13-MAY-92	LETTER from GLAXO to FDA	REQUESTS/COMMENTS REQUESTS/COMMENTS REQUESTS/COMMENTS	MEETING INFO/DETAILS CLINICAL DEVEL PROGRAM PROTOCOL		001
6	21-MAY-92	TELECON from FDA to GLAXO	REQUESTS/COMMENTS	PROTOCOL		
		CSO HIGGINS CALLS CONCERNING PREVIOUS DISCUSSION REGARDING NUMBER OF ECGs WHICH WERE TO BE DONE IN PTCL S3B-201. PREVIOUSLY COMMUNICATED TOTAL WAS NOT WHAT FDA HAD INTENDED AND GLX WILL AGAIN AMEND PTCL WITH FDA DESIRED CHANGES.				
		PROTOCOL: S3B-201 / INV#: / INVESTIGATOR:				
8	29-MAY-92	LETTER from GLAXO to FDA	PRTCL AMND: PROTOCOL CHANGE	PROTOCOL		002

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		AMEND (#1)TO ADD ECGs FOR PTS ON STUDY DAYS 8, 36 & 56 IN ADDTN TO 21 & 49 FROM ORIG PTCL, (#2)MINOR CHANGE IN TERMINOLOGY & (#3)ADDS ECGs FOR EACH PT ON STUDY DAYS 15 & 43 TO BRING TOTAL NUMBER OF ECGs DONE FOR EACH PT DURING CONDUCT OF STUDY TO EIGHT PER RQST OF FDA ON 21-MAY-92.				
		PROTOCOL S2B-201 INV# INVESTIGATOR				
7	09-JUN-92	FAX from FDA to GLAXO	REQUESTS/COMMENTS	FDA REVIEW STATUS		
		FDA COMPLETES RVW OF ORIG APPLICATION AND PTCL S3B-201 MAY BEGIN WITH MODIFICATIONS OF ADDTL ECG's & ONLY 12 PTS ENROLLED AT THIS TIME. DATA FROM THIS STUDY WILL BE RVW'd & FDA CONCURRENCE REC'd BEFORE FURTHER SCHIZOPHRENIA STUDIES MAY PROCEED. NOTE COMMENTS & REQUESTS TO IMPROVE SAFETY OF APPLICATION & NOTE PRECLN CONCERNS FROM INVESTIGATOR's BROCHURE.				
		REFERENCE APPLICATION: IND 39083 — REFERENCE ACT#: 1 — SUP#/SER#: 000 — METHOD OF COMMUNICATION: LETTER from GLAXO to FDA — DOC/ACT DATE: 11-MAR-92				
9	07-JUL-92	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY INCORPORATION BY REFERENCE RESPONSE	TOXICOLOGY TOXICOLOGY TOXICOLOGY		003
		GLX PROVIDES PHARMACOLOGY AND TOXICOLOGY INFORMATION IN RESPONSE TO FDA REQUEST. (WPT/91/409) REPORT FILED ONLY WITH IND 34672, SERIAL #013, AND INCORPORATED BY REFERENCE TO IND 39083, SERIAL #003.				
		REFERENCE APPLICATION: IND 34672 — REFERENCE ACT#: 23 — SUP#/SER#: 013 — METHOD OF COMMUNICATION: LETTER from GLAXO to FDA — DOC/ACT DATE: 07-JUL-92				
		REFERENCE APPLICATION: IND 39083 — REFERENCE ACT#: 7 — METHOD OF COMMUNICATION: FAX from FDA to GLAXO — DOC/ACT DATE: 09-JUN-92				
10	10-AUG-92	TELECON from GLAXO to FDA	TELECONFERENCE	FDA CONSULT/GUIDANCE		

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		CONTACT DR LAUGHREN ABOUT APPROPRIATE EFFICACY SCALES FOR USE IN STUDY OF ACUTE EXACERBATION OF SCHIZOPHRENIA.				
11	21-AUG-92	TELECON from GLAXO to FDA	TELECONFERENCE TELECONFERENCE	FDA CONSULT/GUIDANCE PROTOCOL		
		SPEAK W/CSO HIGGINS REGARDING PTCL VIOLATOR DROPOUT FOR S3B-201. FDA HAS LIMITED ENROLLMENT IN STUDY TO 12 PTS. SINCE STUDY IS A DOULBE-BLIND AND GLX DOES NOT WISH TO BREAK BLIND, THEREFORE GLX PROPOSES THAT FDA ALLOW GLX TO ENROLL A 13TH PATIENT TO INSURE THAT WE HAVE 12 PATIENTS EXPOSED TO GR68755 WHEN WE SUBMIT THE DATA PKG TO FDA FOR RVW. PROTOCOL INV# INVESTIGATOR S3B-201			
12	06-OCT-92	LETTER from GLAXO to FDA	INFO AMND: PHARM/TOXICOLOGY INFO AMND: PHARM/TOXICOLOGY INCORPORATION BY REFERENCE	NON-CLINICAL GENERAL TOXICOLOGY NON-CLINICAL GENERAL		004
		SUBMIT PRELIMINARY INFO FROM FURTHER INVESTIGATIONS OF THE EFFECT OF GR68755 ON HEARING PERFORMED DURING AN ORAL ONCOGENICITY STUDY IN WISTAR RATS & A 12 MONTH ORAL STUDY IN BEAGLE DOGS. File Note: Attachments filed with IND 34,672, Serial #014, Doc Date 06-Oct-92 and incorporated by reference to this IND.				
13	14-JAN-93	LETTER from GLAXO to FDA	INFO AMND: CLINICAL	CLINICAL INCLUSIVE/GENERAL		005
		SUBMIT INTERIM SAFETY RESULTS FROM 13 PATIENTS FROM S2B-201 PER FDA REQUEST OF 09-JUN-92. GLX SEEKS FDA APPROVAL TO ENROLL THE REMAINING 24 PATIENTS AND CONTINUE OUR EARLY PHASE II DEVELOPMENT PROGRAM. PROTOCOL INV# INVESTIGATOR S3B-201				
14	03-FEB-93	LETTER from FDA to GLAXO	RESPONSE	FDA REVIEW STATUS		

Application: IND 39083 GR68755C

ACT#	DOC/ACT DATE	METHOD OF COMMUNICATION	PROCESS	SUBJECT	DCR VOL RANGE	SUP#/ SER#
		FDA COMPLETES RVW OF SUBMISSION AND CONCLUDE THAT IT IS REASONABLY SAFE FOR THE ENROLLMENT OF THE REMAINING 24 PATIENTS IN PTCL S3B-201.				
		REFERENCE APPLICATION: IND 39083	REFERENCE ACT#: 13	SUP#/SER#: 005	METHOD OF COMMUNICATION: LETTER from GLAXO to FDA	DOC/ACT DATE: 14-JAN-93
15	12-MAY-93	LETTER from GLAXO to FDA	ANNUAL REPORT (IND)	INVESTIGATOR BROCHURE		006
			ANNUAL REPORT (IND)	CLINICAL DEVEL PROGRAM		
			ANNUAL REPORT (IND)	CLINICAL STUDY STATUS		
			ANNUAL REPORT (IND)	SAFETY		
			ANNUAL REPORT (IND)	NON-CLINICAL GENERAL		
		COVERING PERIOD MARCH, 1992 TO MARCH, 1993.				
16	18-FEB-94	LETTER from GLAXO to FDA	GENERAL CORRESPONDENCE	STUDY REPORT		007
		PROVIDE FINAL STUDY REPORT UCP/92/019 (PROTOCOL S3A-102). File Note: The attachments to this submission are filed to IND 34,672, Serial #018, ONLY. Also this submission was sent to the FDA, but no copies were sent to the DCR. The FDA sent us back a copy.				
		PROTOCOL: S3A-102	INV#:	INVESTIGATOR:		
17	08-JUN-94	LETTER from GLAXO to FDA	ANNUAL REPORT (IND)	SAFETY		008
			ANNUAL REPORT (IND)	NON-CLINICAL GENERAL		
			INACTIVATES IND	UPDATE		
		SUMMARY OF PROGRESS OF INVESTIGATIONS DURING INTERVAL MARCH, 1993 THROUGH MARCH, 1994. ALSO RQST THAT THIS IND BE PUT ON INACTIVE STATUS. THERE ARE NO PLANS FOR ADDTL DEVELOPMENT ACTIVITY OF THIS COMPOUND AND NO PATIENTS HAVE BEEN ENTERED INTO CLN TRIALS UNDER THIS IND SINCE FEB, 93. ALSO NOTE THAT IND 34,672 WILL BE INACTIVATED AT THE TIME OF ITS ANNUAL RPT.				

EXHIBIT 9C

Document Chronology / Due Diligence Logs for

IND No. 45,128

Regulatory Affairs
CARDS
Chronology

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-Mar-1994	Glaxo Wellcome Correspondence	General Correspondence	Transfer of Ownership	

General Correspondence: Letter of Authorization for reference of a Sponsor/Investigator IND

22-Apr-1994	Correspondence	Initial Investigational New Drug Application		0000

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea
Initial Investigational New Drug Application
Serial No.: 0000

28-Apr-1994	Food and Drug Administration Correspondence	Acknowledgement	IND # Assigned	

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea
Acknowledgement: IND # Assigned

09-Aug-1994	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea
Comment/Information Request: Clinical

22-Sep-1994	Correspondence	Protocol Amendment: Change in Protocol Response to FDA Request/Comment	Clinical Clinical	0001

IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea
Protocol Amendment: Change in Protocol, Clinical
Response to FDA Request/Comment: Clinical
Serial No.: 0001

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
01-Dec-1994	Correspondence	Protocol Amendment: Change in Protocol	Clinical	0002
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: Change in Protocol Serial No.: 0002			
31-Jan-1995	Food and Drug Administration Correspondence	Comment/Information Request	Clinical Nonclinical Protocol	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Comment/Information Request: Clinical, Nonclinical			
16-Feb-1995	Correspondence	Protocol Amendment: Change in Protocol	Clinical	0003
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: Change in Protocol Serial No.: 0003			
20-Mar-1995	Correspondence	Protocol Amendment: Change in Protocol Response to FDA Request/Comment	Clinical Nonclinical	0004
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: Change in Protocol Response to FDA Request/Comment: Nonclinical Serial No.: 0004			
24-Apr-1995	Correspondence	Information Amendment: Nonclinical Response to FDA Request/Comment	Nonclinical	0005

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Information Amendment: Nonclinical Response to FDA Request/Comment Serial No.: 0005			
28-Apr-1995	Food and Drug Administration Telephone Conversation	Comment/Information Request	Nonclinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea GW contacted in requards to non-clinical rat studies (two year rat & mouse oncology studies and 12 month rat study)			
01-May-1995	Correspondence	Information Amendment: Clinical	Safety	0006
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Information Amendment: Clinical Serial No.: 0006			
01-May-1995	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Nonclinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Response to FDA Request/Comment: Nonclinical			
02-May-1995	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Comment/Information Request: Clinical			

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-May-1995	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Comment/Information Request: Clinical			
12-May-1995	Correspondence	Protocol Amendment: Change in Protocol	Clinical	0007
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: Change in Protocol Serial No.: 0007			
07-Aug-1995	Correspondence	Protocol Amendment: New Investigator		0008
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Protocol Amendment: New Investigator Serial No.: 0008			
07-Aug-1995	Correspondence	Annual Report		0009
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Annual Report Serial No.: 0009			
06-Mar-1996	Correspondence	10-Day ADR Report		0010
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea 10-Day ADR Report Serial No.: 0010			

Reg ory Affairs
CARDS
Chronology

Application: IND 45128; GR68755 Tablets treatment of Carcinoid Diarrhea
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Aug-1996	Correspondence	Annual Report Request to Withdraw		0011
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Annual Report Request to Withdraw Serial No.: 0011			
24-Nov-1997	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Comment/Information Request			
23-Dec-1997	Food and Drug Administration Correspondence	Acknowledgement	Withdrawal	
	IND 45,128; GR68755 Tablets treatment of Carcinoid Diarrhea Acknowledgement: Withdrawal			

EXHIBIT 9D

Transcript of Dr. Camilleri's remarks before the Gastrointestinal Drugs Advisory Committee

[--- Unable To Translate Box ---]

VRDEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

GASTROINTESTINAL DRUGS ADVISORY COMMITTEE

Tuesday, November 16, 1999

9:00 a.m.

Holiday Inn
2 Montgomery Village Avenue
Gaithersburg, Maryland

MILLER REPORTING COMPANY, INC.
507 C Street, N.E.
Washington, D.C. 20002
(202) 546-6666

COMMITTEE MEMBERS PRESENT:

STEPHEN D. HANAUER, M.D., Chairman

ROSEMARY BERARDI, Pharm. D.

GEORGE D. FERRY, M.D.

NANCY L. GELLER, Ph.D.

LOREN LAINE, M.D.

JOANNE A. WILSON, M.D.

C O N T E N T S

P R O C E E D I N G S

CHAIRMAN HANAUER: I'd like to welcome you to this morning's meeting. It's obviously going to be an important Advisory Committee meeting, probably precedent-setting, depending upon the--well, in any event, on the outcome of the Committee's thinking process regarding this.

My name is Steve Hanauer. I'm from the University of Chicago, and I'm the Chairman of the GI Drugs Advisory Committee. To begin with, I'd like to have an introduction of those of us at the table. Perhaps we'll start on this end with Dr. Senior, introducing ourselves to the audience.

DR. SENIOR: I'm John Senior. I'm a GI medical reviewer at the FDA.

DR. HOUN: I'm Florence Houn. I'm the Office Director for the Office of Drug Evaluation III at FDA.

DR. TALARICO: I'm Lilia Talarico. I'm the Director of the Division of GI and Coagulation Drug Products.

DR. WALD: I'm Arnold Wald. I'm from the University of Pittsburgh Medical Center.

DR. BERARDI: I'm Rosemary Berardi and I'm from the College of Pharmacy at the University of Michigan, and I'm the consumer representative to this Committee.

DR. LAINE: I'm Loren Laine and I'm from USC Medical School, in Los Angeles, gastroenterology.

DR. WILSON: I'm Joanne Wilson. I'm at Duke University Medical Center, gastroenterology.

MS. STANDAERT: I'm Joan Standaert, the Executive Secretary of the Committee.

DR. FERRY: I'm George Ferry, pediatric gastroenterology, from Baylor College of Medicine, in Houston.

DR. GELLER: I'm Nancy Geller. I'm Director of the Office of Biostatistics Research at the National Heart, Lung, and Blood Institute, in Bethesda.

DR. RACZKOWSKI: To my left will be Dr. Robert Prizont, who is a medical reviewer from the Division of Gastrointestinal Drug Products. I am Dr. Victor Raczkowski, the Deputy Office Director in the Office of Drug Evaluation III.

DR. GALLO-TORRES: I'm Dr. Hugo Gallo-Torres. I am the Medical Team Leader of the reviewing division, the Division of Gastrointestinal and Coagulation Drug Products.

CHAIRMAN HANAUER: And at this point, Joan Standaert is going to read a statement regarding conflict of interest.

MS. STANDAERT: The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants, it is has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research which have been reported by the participants present no potential for an appearance of a conflict of interest at this meeting, with the following exceptions.

In accordance with 18 U.S.C. 208(b), full waivers have been granted to Dr. Loren A. Laine and Dr. George D. Ferry which permit them to participate in all official matters concerning Lotronex. A copy of these waivers may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building. We would also like to disclose for the record that Dr. William M. Steinberg will be excluded from participating in all matters pertaining to Glaxo Wellcome's Lotronex.

With respect to FDA's invited guests, there are reported interests which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Arnold Wald would like to disclose for the record that he was an investigator on alosetron, but not the principal investigator. He also has a grant from Glaxo on a matter unrelated to alosetron.

In the event that the discussions involve any

other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record. With respect to all other participants, we ask, in the interest of fairness, that they address any current or previous financial involvement with any firm whose products they may wish to comment upon.

That concludes the statement for this meeting.

CHAIRMAN HANAUER: Anyone else want to comment regarding that?

[No response.]

CHAIRMAN HANAUER: Okay. For each of these Committee meetings, there is an opportunity for the public to make any comments, and at this point we've been notified that there are two individuals who represent the International Foundation for Functional Gastrointestinal Disorders who would like to speak.

I would like to invite Nancy Norton to make the initial comments.

MS. NORTON: Thank you. Good morning, Members of the Committee. Thank you for the opportunity to appear before you today. I am the founder and President of the International Foundation for Functional Gastrointestinal Disorders and the current Chairman of the Digestive Disease

Thank you.

CHAIRMAN HANAUER: The next speaker is Dr. Camilleri, from the Mayo Clinic.

DR. CAMILLERI: Good morning, Dr. Hanauer, Members of the Committee, Ladies and Gentlemen. My task this morning is to review for you the rationale for treatment of IBS with alosetron, a 5HT3 antagonist. The specific objectives which I hope to cover are the role of serotonin in disease, and I shall give examples of the role of serotonin in irritable bowel syndrome and in carcinoid diarrhea; and, secondly, to review the pharmacodynamic studies that provide the rationale for these 5HT3 antagonists in IBS, specifically the effects on motility, secretion, and sensation.

In a recently published study from Mike Farthing's group in Britain, it was demonstrated that patients with irritable bowel syndrome have post-prandial 5HT levels which are higher than those of healthy controls. Now, the prototype disease that is associated with high pre- and post-prandial levels of 5HT in the circulation is carcinoid diarrhea. This is a severe diarrhea that is associated with a neuroendocrine tumor in which the tumor produces a large amount of serotonin, among other transmitters, and this serotonin spills over into the peripheral plasma and has effect on the way in which the bowel functions.

Indeed, in order to study these patients, we had to develop some novel methodology that allows us to objectively quantify the changes in motor function in the gastrointestinal tract. These novel methodologies are summarized in this slide. Using a gamma camera, and therefore a non-invasive technique, we are able to radio-label a meal and watch and quantitate the rate of emptying from the stomach and from the small intestine of that radio-labeled meal.

At the same time, we provide a different isotope delivered to the distal small intestine in a special methacrylate-coated polymer which dissolves in the distal small intestine, thereby liberating isotope, which then gives us an image of the content moving through the different segments of the colon. And on the next slide you will see that we have illustrated on an actual scan the proportion of isotope in different segments of the colon.

So here's an example of a patient who has carcinoid diarrhea, and we're seeing the isotope located in the different sections of the colon. This isotope is located in the descending colon about one hour after the meal was ingested. Two hours later, most of that isotope has not reached the rectum and is ready for expulsion because of a significant diarrhea.

Now, this is a process that would normally would

take between 25 and 35 hours, and I would emphasize the point that this has occurred in about 3 hours. Therefore, carcinoid diarrhea is associated with rapid emptying of the proximal colon. Quantitative data show that this rate of emptying is about six times that of healthy controls. We also see on this slide that the small bowel transit time is reduced partly as a result of a stimulation of motor function and partly because of the hyper secretion of fluid and electrolytes into the intestine as a result of the serotonin stimulation in the small intestine of these patients.

I would like now to review briefly the pharmacodynamic studies in humans that suggest that the 5HT3 approach would relieve diarrhea and pain, specifically through changes in motor function, fluid and electrolyte absorption, and changes in sensation. Let's first concentrate on the effects of alosetron on motility.

In a study performed by Whorwell and his colleagues in Manchester, United Kingdom, alosetron effect on colonic transit was evaluated in 12 patients with irritable bowel syndrome. This was a randomized double-blind placebo-controlled crossover study in which the dose of 2 milligrams twice a day of alosetron was evaluated. The method used to evaluate transit involved a common and well-validated system, which is the radiopaque marker

transit method. Note here that the alosetron treatment was associated with an increase in the colonic transit time, and that this was predominantly an effect on the left side of the colon.

In studies that we have performed at Mayo Clinic on the effect of alosetron on colonic transit and other parameters in carcinoid diarrhea, we have noted that an increase in the dosage of alosetron, .5 milligrams twice a day to 2 milligrams twice a day, results in a significant three-fold to four-fold reduction in the rate of emptying of the proximal colon. This is associated with a trend in the reduction of 24-hour stool weight in the patients with carcinoid diarrhea.

One of the secondary parameters that we evaluated in that clinical study which consisted of three weeks of treatment with alosetron was to determined the number of tablets of Loperamide that were required as rescue for the control of diarrhea. In patients with carcinoid diarrhea, diarrhea so severe that the patients need to carry an anti-diarrheal with them--and we quantified the number of Loperamide tablets used in this three-week period of time.

Notice in this graph that we have tabulated the cumulative percentage of patients who required equal to or more than five tablets of Loperamide over this three-week period. Notice also that the proportion of patients

requiring rescue with Loperamide decreases with increasing dosage of alosetron in this three-week trial.

What about fluid and electrolyte secretion? In a classical methodology study, Farthing's group has performed triple lumen profusion studies using a 30-centimeter isolated jejunal segment with occluding balloons at each end and the classical marker 14carbon-PEG 4000 as a marker of fluid and electrolyte flux.

Notice that absorption is above the zero line and secretion is below the zero line for both fluid flux and sodium flux. Normally, the small intestine is in a state of absorption for both sodium and for water, as shown by the bar and whisker plot in yellow. Alosetron resulted in an increase in the fluid flux and sodium flux in the absorptive sense, therefore suggesting that alosetron would have an effect in facilitating greater absorption of water and salts in the small intestine in humans.

Finally, let us review briefly some of the studies looking at the effect of alosetron on sensation. In this study by Michel Delvaux and his colleagues, in Toulouse, France, the colon sensation was evaluated by means of a balloon which was placed inside the left part of the colon. Now, in these experiments the volume in order to induce perception of this distension stimulus and the volume to induce a sensation of pain in response to distension is

being recorded and monitored to evaluate the threshold for sensation.

Note that alosetron at these two dosages studied resulted in an increase in the volume to reach perception and an increase in the volume to reach pain threshold, suggesting that the sensitivity of the bowel was being reduced by that treatment. This study, incidentally, was performed in patients with irritable bowel syndrome.

Part of the effect of that change in threshold, that increase in threshold in response to alosetron can be explained by a change in the compliance of the colon. Here, there's an increase in pressure imposed on that segment of colon that is being evaluated. The volume of that segment of colon measured by means of this intracolonic balloon is increased, suggesting that the colon is more compliant; it is able to accommodate a greater volume, for instance, from gas in this case, but presumably also from more solid or liquid components of colonic residue or content.

So, in summary, you've heard that 5HT3 receptors are involved in visceral sensory, secretory, and motor processes in the gastrointestinal tract. Alosetron, which is a selective and potent 5HT3 receptor antagonist, decreases sensitivity to colonic distension, enhances jejunal water and sodium absorption, and slows colonic transit.

I thank you for your attention.

CHAIRMAN HANAUER: Thank you.

The last of the first series of speakers on behalf of Glaxo is Dr. Lin Chang, from UCLA.

DR. CHANG: Good morning. I'm going to speak today about gender differences in gastrointestinal physiology and disease, and particularly focus on irritable bowel syndrome, or IBS.

As you heard earlier from Dr. Wood, irritable bowel syndrome is predominantly seen in females. And there are other chronic pain disorders that are also seen in females more often than in males, and these include chronic constipation, fibromyalgia, chronic fatigue syndrome, interstitial cystitis, migraine headaches, and temporal mandibular joint disorder. These pain disorders share common clinical characteristics and can typically overlap in the same patient, and it has been hypothesized that these chronic pain disorders share a common etiology.

Before I review the gender differences in physiology, I wanted just to review the dimensions of the response to a painful or noxious stimulus. These dimensions include sensory ratings which measure the intensity of a stimulus, affective ratings which measure unpleasantness of a stimulus. There's cognitive, evaluative, physiological and behavioral responses that all contribute to the pain

EXHIBIT 9E

Document Chronology / Due Diligence Logs for

IND No. 48,487

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Aug-1995	Glaxo Wellcome Correspondence	Initial Investigational New Drug Application	CMC Protocol(s) Included Study Reports	0000

GR68755 (alosetron hydrochloride) Tablets
Initial Investigational New Drug Application
Serial No.: 000

Protocol with Report(s):
C92-006 with:
GCP/92/006
C92-019 with:
GCP/92/019
C92-087 with:
GCP/92/087
G91-019 with:
GMH/91/051
GCP92057 with:
GMH/92/057
GHP8917 with:
GMH/91/025
GHP8923 with:
GMH/89/024
GHP8938 with:
GMH/90/004
GHP8944 with:
GPK/91/005
GHP9005 with:
GMH/90/012
GHP9016 with:
GMH/91/007
GHP9021 with:
GMH/91/002
GPH9027 with:
GMH/91/015
GPK9001 with:
GPK/90/006

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
GPK9002 with:				
GPK/90/008				
S3B101 with:				
UCP/91/014				
S3B102 with:				
UCP/92/019				
S3B201 with:				
UCP/93/09				
S3BB2001 with:				
GGN/93/010				
S3BB2002 with:				
GGN/93/011				
S3BB2003 with:				
GGN/93/012				
S3BB2004 with:				
GGN/93/013				
S3BB2009 with:				
GGN/94/022				

Report: NYP/95/001, WBP/89/060, WBP/89/062, WBP/89/071, WBP/89/097, WBP/89/100, WBP/89/101, WBP/90/041, WBP/90/052, WBP/90/055, WBP/90/056, WBP/90/057, WBP/90/062, WBP/90/063, WBP/90/069, WBP/90/073, WBP/90/097, WBP/90/099, WBP/91/008, WBP/91/017, WBP/91/041, WBP/91/044, WBP/91/045, WBP/91/046, WBP/91/047, WBP/91/098, WBP/91/099, WBP/91/105, WBP/91/108, WBP/92/021, WBP/92/088, WBP/92/129, WBP/93/019, WBP/93/029, WBP/94/012, WBP/94/037, WBP/95/042, WBP/95/048, WGP/90/001, WGP/93/021, WMP/91/049, WNP/88/022, WNP/89/056, WNP/89/057, WNP/89/058, WNP/89/059, WNP/89/069, WNP/90/004, WNP/90/005, WNP/90/006, WNP/90/007, WNP/90/008, WNP/90/017, WNP/92/060, WNP/93/008, WPC/88/006, WPC/89/016, WPT/88/069, WPT/89/103, WPT/89/188, WPT/89/202, WPT/89/211, WPT/89/214, WPT/89/218, WPT/89/237, WPT/89/242, WPT/89/244, WPT/89/247, WPT/89/249, WPT/89/250, WPT/89/271, WPT/89/282, WPT/89/328, WPT/89/330, WPT/90/014, WPT/90/131, WPT/90/161, WPT/90/163, WPT/90/164, WPT/90/188, WPT/90/302, WPT/90/304, WPT/91/012, WPT/91/024, WPT/91/058, WPT/91/164, WPT/91/409, WPT/92/025, WPT/92/095, WPT/92/325, WPT/93/134, WPT/93/360, WPT/93/503

14-Aug-1995 Food and Drug Administration Correspondence Acknowledgement IND # Assigned

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Acknowledgement: IND # Assigned

Protocol: S3BA2001

21-Sep-1995 Glaxo Wellcome Telephone Conversation General Teleconference Clinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Teleconference: Clinical

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
05-Dec-1995	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0002
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 002			
05-Dec-1995	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0001
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 001			
02-Jan-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0003
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 003			
22-Jan-1996	Glaxo Wellcome Correspondence	Response to FDA Request/Comment		0004
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Response to FDA Request/Comment Serial No.: 004			
31-Jan-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0005

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 005			
19-Feb-1996	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol		0006
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 006			
28-Feb-1996	Glaxo Wellcome Correspondence	General Correspondence		0007
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence; Withdrawal of Request for Waivers Serial No.: 007			
13-Mar-1996	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator		0008
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 008			
10-Apr-1996	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator		0009
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 009			
19-Apr-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls		0010
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Information Amendment: Chemistry Manufacturing and Controls Serial No.: 010			
15-May-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0011
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 011			
18-Jun-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0012
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 012			
18-Jul-1996	Food and Drug Administration Correspondence	Comment/Information Request	Nonclinical	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) FDA Comment			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
25-Jul-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0013
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 013			
09-Aug-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0014
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 014			
04-Sep-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0015
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 015			
13-Sep-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0016
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 016			
01-Oct-1996	Glaxo Wellcome Correspondence	Annual Report	Foreign Marketing Developments	0017

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; Alosetron (GR68755) Tablets Annual Report Serial No.: 017			
13-Nov-1996	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0018
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 018			
22-Nov-1996	Glaxo Wellcome Correspondence	General Correspondence		0019
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Serial No.: 019			
23-Jan-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0020
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 020			
04-Mar-1997	Glaxo Wellcome Correspondence	General Correspondence	Meeting Request	0021
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Meeting Request - End of Phase II Serial No.: 021			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
28-Mar-1997	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls		0022
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Request for Comment Concerning NDA Stability Program Proposal Serial No.: 022			
15-Apr-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator		0023
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 023			
07-May-1997	Glaxo Wellcome Correspondence	General Correspondence		0024
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Background Information for End-of-Phase II Meeting (30 May 1997) Serial No.: 024			
28-May-1997	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls		0025
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 025			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
30-May-1997	Glaxo Wellcome Trip Report	Type	End of Phase II Meeting	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Type: End of Phase II Meeting			
02-Jun-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0026
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 026			
27-Jun-1997	Food and Drug Administration Correspondence	Minutes of Meeting	End of Phase II Meeting	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: End of Phase II Meeting			
10-Jul-1997	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls		0027
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 027			
11-Jul-1997	Glaxo Wellcome Correspondence	General Correspondence		0029

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Serial No.: 029			
31-Jul-1997	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Labeling of Clinical Supplies	General Teleconference	CMC	
07-Aug-1997	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence Serial No.: 030	General Correspondence	CMC	0030
07-Aug-1997	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 031	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0031
28-Aug-1997	Food and Drug Administration Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) Comment/Information Request	Comment/Information Request		

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Sep-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0032
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 032			
23-Sep-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0033
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 033 Protocol Amendment: New Investigator			
Protocol: S3BA3001, S3BA3002				
26-Sep-1997	Glaxo Wellcome Correspondence	Annual Report	Adverse Event Summary Clinical Study Information CMC Outstanding Regulatory Business	0034
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Annual Report (5-Aug-96 through 4-Aug 97) Serial No.: 034			
Comment: 5-Aug-96 through 4-Aug-97				
26-Sep-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0035
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 035			
Protocol: S3BB1011 Protocol with Investigator(s):				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
S3BB1011 with: Aziz L Laurent, M.D.				
01-Oct-1997	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) Response to FDA Request/Comment: CMC	General Teleconference	CMC	
03-Oct-1997	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator, Investigator Add, Other 1572 Change Serial No.: 036	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0036
Protocol with Investigator(s): S3BA3001 with: Hector D Allende, M.D., Caroline T Diamant, M.D., Michael T Draelos, M.D., Robert M Finlaw, M.D., Gregory Fusilier, M.D., Stephen L Green, M.D., Keith P Hussey, M.D., Adesh K Jain, M.D., Steven Krumholz, M.D., Oscar Martinez, M.D., Daniel J Pambianco, M.D., Peter M Pardoll, M.D. S3BA3002 with: Raymond L Bell, M.D., Dale Collins, M.D., Michael G DeLissio, M.D., Ervin Eaker, M.D., John K Earl, M.D., Michael F Elmore, M.D., Duane D Fitch, M.D., Martin D Gelfand, M.D., Arthur Green, D.O., Daniel E Gremillion, M.D., Paula H Hall, M.D., David A Johnson, M.D., Howard M Kenney, M.D., Robert D Lerner, M.D., Robert L Lindenberg, M.D., James H Linne, M.D., Dennis C. McCluskey, M.D., V C Motaparthy, M.D., Linda P Murray, M.D., Jansi Prabakaran, M.D., Lee R Rocamora, M.D., Charles W Scrowcroft, M.D., David R Silvers, M.D., Michael Stadiem, M.D., Martin L Throne, M.D., John A Walker, M.D., Gilbert Weisman, DO			
09-Oct-1997	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Request for Review of Lotronex as the Proprietary Name for Alosetron Serial No.: 037	General Correspondence	Other	0037
14-Oct-1997	Glaxo Wellcome Correspondence	Amendment: Other	Change in Medical Monitor CRO	0038

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Transfer of Obligations to Contract Research Organization Serial No.: 038			
Protocol: S3BA3001, S3BA3002 Comment: Study S3BA3001conducted by ClinTrials Research Inc.; Study S3BA3002 conducted by ICON Clinical Research; Statistical/pharmacoeconomic analyses for Studies S3BA3001 and S3BA3002 performed by Quintiles, Inc.; Medical and Safety Monitor: Allen Mangel				
23-Oct-1997	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol		0039
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 039			
Protocol with Amendment(s): S3BB1011 with: 01				
03-Nov-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	 Investigator Add	0040
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 040			
Protocol with Amendment(s): S3BA3003 with: 01 Investigator: Brandon, Milan				
06-Nov-1997	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	 Investigator Add Other 1572 Change	0041
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Protocol Amendment: New Investigator
Serial No.: 041

Protocol: S3BA2003
Protocol with Amendment(s):
S3BA2002 with:
03
Protocol with Investigator(s):
S3BA3001 with:
Gary M Barton, M.D., Robert Burakoff, M.D., Jack A DiPalma, M.D., Robert L Frachtman, M.D., Alan Graff, M.D., Michael R Grossman, M.D., Mario D Kamionkowski, M.D., Rashid A Khairi, M.D., Donald F Kirby, M.D., Terry D. Klein, M.D., Daniel M Kruss, M.D., Susan Lepinski, M.D., Robert S Lipetz, M.D., David G Mangels, M.D., Antoinette Mangione, M.D., James McGill, M.D., William S Mullican, M.D., Zev Munk, M.D., Mark Murphy, M.D., Clinton D Polhamus, M.D., Ronald E Pruitt, M.D., Michael Safdi, M.D., William J Semon, M.D., Howard I Siegel, M.D., Lewis Strong, M.D., Robert E Tepper, M.D., Salam Zakko, M.D., Marc J Zuckerman, M.D.
S3BA3002 with:
Greg Donald Anderson, M.D., Charles K Bedard, M.D., Scott D Bleser, D.O., Yang K Chen, M.D., Gregory V. Collins, M.D., Raquel Croitoru, M.D., Byron L Cryer, M.D., W. Travis Ellison, M.D., John Gray, M.D., Philip E Jaffe, M.D., David S James, DO, Frank J Konicek, M.D., Mark E Mailliard, M.D., Thomas McDonald, M.D., Trent W Nichols, M.D., Alan Plotner, M.D., Ronald Scott Powell, M.D., Sanjeeva T Reddy, M.D., Michael D Schiff, M.D., Ann L Silverman, M.D., Roger D Soloway, M.D., Marybeth Spanarkel, M.D., Richard S Sprague, M.D., Bruce E Stein, M.D., Craig W Wiesenhutter, M.D., Richard A Wright, M.D.

02-Dec-1997	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0042

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 042

Protocol with Investigator(s):
S3BA3001 with:
Matthew R. Astroff, M.D., D Eric Bolster, M.D., Mark H Bowles, M.D., Howard B Chodash, M.D., Fabio Cominelli, M.D., Vincent A DeLuca, M.D., Sudhir K Dutta, M.D., Robert M. Eisdorfer, M.D., Mark Eisner, M.D., Jay L Goldstein, M.D., M Scott Harris, M.D., John M Inadomi, M.D., Ronica Kluge, M.D., David G Kogut, M.D., Richard A Krause, M.D., Thomas F Lansdale, M.D., Paul J Lebovitz, M.D., Mark Lott, M.D., Bruce Luxon, M.D., Richard B Lynn, M.D., William Murchison, M.D., Martin Poleski, M.D., Peter M. Ripley, M.D., Ronald Schwarz, M.D., William Wilder, M.D.
S3BA3002 with:
William Y Chey, M.D., Alan Cutler, M.D., Ben J Dolin, M.D., Shaban Faruqui, M.D., Richard G Free, M.D., Louis J Gringeri, M.D.
S3BA3003 with:
Scott D Bleser, D.O., Milan Brandon, M.D., Eugene J Burbige, M.D., Rokay Kamyar, M.D., Chester W Kessler, M.D., Michael Kurtz, M.D., James Lewis, M.D., Peter L Moses, M.D., Thomas J Pulliam, M.D., Patrick Schow, M.D.

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Dec-1997	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol		0043

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 043

Protocol with Amendment(s):
S3BA3002 with:
01

15-Jan-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0044

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 044

Protocol with Investigator(s):
S3BA3001 with:
Lin Chang, M.D., Edward H Cheng, M.D., Douglas A Drossman, M.D., Ronald Fogel, M.D., Oliver D Gilliam, M.D., Peter J Gulden, M.D., Ross A Kommor, M.D., Robert B Lasser, M.D., Michael J Lawson, M.D., Philip B Miner, M.D., Joseph L Nelson, M.D., John Leonard Petrini, M.D., David B Stanton, M.D., Keith G Tolman, M.D., Gregg A Valenzuela, M.D.
S3BA3002 with:
Jeffrey D Feldstein, M.D., Joseph X Jenkins, M.D., Michael Opipari, M.D., Bennett H Plotnick, M.D., Eamonn M Quigley, M.D., Jean-Pierre Raufman, M.D., W Harley Sobin, M.D.
S3BA3003 with:
Richard D. Baerg, M.D., William R. Berry, M.D., Larry R Cain, M.D., Jacques R. Caldwell, M.D., Charles Casale, M.D., Selwyn A Cohen, M.D., Charles L Colip, M.D., Dale Collins, M.D., James L Conrad, M.D., Charles H DeBusk, M.D., Michael G DeLissio, M.D., Michael F Elmore, M.D., James I Fidelholtz, M.D., Martin D Gelfand, M.D., Daniel E Gremillion, M.D., H Freeman Harris, M.D., William H Holderman, M.D., Robert Holmes, M.D., Dennis C. McCluskey, M.D., Linda P Murray, M.D., Mario Z Rosenberg, M.D., Thomas Rosenfield, M.D., Stephen C Schindler, M.D., Michael Stadiem, M.D., James R Wagner, M.D., John A Walker, M.D., Steven J Wegley, M.D., Gerald D Wolfley, M.D., James D Wolosin, M.D.

19-Feb-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0045

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 045

Protocol with Investigator(s):
S3BA3001 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

David R Cave, M.D., James N Cooper, M.D., M Brian Fennerty, M.D., Charles Melburn Wilcox, M.D.
S3BA3002 with:
Robert Bruce Cameron, M.D., Ronnie Fass, M.D., Bruce Jones, M.D., Arthur J McCullough, M.D., Frederick Wilson, M.D.
S3BA3003 with:
Charles K Bedard, M.D., Roland William Bennetts, M.D., Charles Casale, M.D., David S James, DO, Thomas Loludice, M.D., William B Smith, M.D.

18-Mar-1998	Food and Drug Administration Correspondence	General Correspondence	Status Update	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence: No Objections With Proprietary Name, Lotronex

20-Mar-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0046

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 046

Protocol with Amendment(s):
S3BA2002 with:
04

27-Mar-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0047

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 047

Protocol: S3BA3001
Protocol with Investigator(s):
S3BA3002 with:
Patricia Raymond, M.D.
S3BA3003 with:
Jim Bauer, M.D., John W Beckman, M.D., Philip C Bird, M.D., William Y Chey, M.D., Michael T Draelos, M.D., John K Earl, M.D., Robert M Finlaw, M.D., Richard Fisher, M.D., Duane D Fitch, M.D., Walter N Gaman, M.D., Michael W Gorsky, M.D., Russell Graham, M.D., Stephen L Green, M.D., Paula H Hall, M.D., Charles D Hanshaw, M.D., R Bruce Johnson, M.D., John J Jolley, M.D., Lloyd King, M.D., Ross A Kommor, M.D., Mark Lamet, M.D., Robert D Lerner, M.D., David J Miller, M.D., S. David Miller, M.D., Oscar

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Oandasan, M.D., David J Sales, M.D., Douglas Schumacher, M.D., B.N. Shivakumar, M.D., James D Torosis, M.D.				
10-Apr-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Investigator Add Other 1572 Change	0048

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 048

Protocol with Amendment(s):
S3BA3002 with:
02
S3BA3003 with:
02, 03
Protocol with Investigator(s):
S3BA3001 with:
Gordon V Ohning, M.D.
S3BA3003 with:
Arthur Green, D.O., Bruce Jones, M.D., Steven Krumholz, M.D., David G Mangels, M.D., Frederick H Opper, M.D., Alan Plotner, M.D., Ronald Scott Powell, M.D., Jansi Prabakaran, M.D., Fred Rosenberg, M.D., Ronald Schwarz, M.D., Charles W Scrowcroft, M.D., Bruce E Stein, M.D., William R Stern, M.D., Gilbert Weisman, DO, Barry D Winston, M.D., Marc J Zuckerman, M.D.

06-May-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0049

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 049

Protocol: S3BA3001, S3BA3002
Protocol with Investigator(s):
S3BA3003 with:
Charles Franklin Barish, M.D., Thomas D Bianchi, M.D., Jeffrey R Breiter, M.D., Ben J Dolin, M.D., W. Travis Ellison, M.D., Robert L Frachtman, M.D., Gregory Fusilier, M.D., Oliver D Gilliam, M.D., David A Johnson, M.D., Rashid A Khairi, M.D., Sidney F Lauteria, M.D., James McGill, M.D., William S Mullican, M.D., Mark Murphy, M.D., Daniel J Pambianco, M.D., Adisesha B Reddy, M.D., Sanjeeva T Reddy, M.D., Herbert Rubin, M.D., Michael D Schiff, M.D., Patrick Schow, M.D., Salam Zakko, M.D.

11-May-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0051

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 051			
Protocol: S3BA3003 ADR: A0064427A				
12-May-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0050
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 050			
Protocol with Amendment(s): S3BA3002 with: 03				
04-Jun-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0052
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 052			
Protocol: S3BA3003 ADR: A0064427A				
10-Jun-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol		0053
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 053			
Protocol with Amendment(s): S3BA3001 with: 01, 02, 03				
18-Jun-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0055

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 055			

Protocol: S3BA3001
Protocol with Investigator(s):
S3BA3003 with:
Fabio Cominelli, M.D., Raquel Croitoru, M.D., Vincent A DeLuca, M.D., Michael R Grossman, M.D., M Scott Harris, M.D., David G Kogut, M.D., George Koval, M.D., Richard A Krause, M.D., Daniel M Kruss, M.D., Michael S Levine, M.D., Robert L Lindenberg, M.D., James H Linne, M.D., Oscar Martinez, M.D., Thomas McDonald, M.D., Michael Opipari, M.D., Stephen D Pershing, M.D., Bennett H Plotnick, M.D., Ronald E Pruitt, M.D., Ann L Silverman, M.D., Eugene Spiotta, M.D., Lewis Strong, M.D., Robert E Tepper, M.D., M. Scott Touger, M.D., Craig W Wiesenhutter, M.D.

18-Jun-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0054
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 054			

Protocol with Amendment(s):
S3BA3003 with:
04

24-Jun-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0056
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 056			

Protocol with Investigator(s):
S3B30004 with:
Douglas A Drossman, M.D.

13-Jul-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add Other 1572 Change	0057

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 057			

Protocol with Amendment(s):
S3BA3002 with:
04
Protocol with Investigator(s):
S3BA3003 with:
Sudhir K Dutta, M.D., Paul J Lebovitz, M.D., Peter L Moses, M.D., Gordon V Ohning, M.D., Clinton D Polhamus, M.D., Richard A Wright, M.D.

16-Jul-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0058
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 058			

Protocol: S3BA3003
ADR: A0064427A

17-Jul-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol		0059
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 059			

Protocol with Investigator(s):
S3B20013 with:
William Y Chey, M.D.

22-Jul-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0060
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 060			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol: S3BA3003 ADR: A0067942A				
23-Jul-1998	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0061
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls Serial No.: 061			
27-Jul-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator		0063
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 063			
Protocol with Investigator(s): S3BA1006 with: William Y Chey, M.D.				
27-Jul-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol		0062
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 062			
Protocol with Amendment(s): S3BA1002 with: 01, 02 Protocol with Investigator(s): S3BA1002 with:				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Samuel Serfaty, M.D.				
04-Aug-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0064
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 064			
Protocol: S3BA3002 Protocol with Amendment(s): S3BA1002 with: 02 Protocol with Investigator(s): S3BA3001 with: David George Scholz, M.D. S3BA3003 with: Thomas Anthony Carr, M.D., Robert Murphy, M.D.				
17-Aug-1998	Glaxo Wellcome Telephone Conversation	General Teleconference		
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference			
31-Aug-1998	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details Meeting Request	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Memorandum: Meeting Request			
02-Sep-1998	Glaxo Wellcome Correspondence	Annual Report	Adverse Event Summary Clinical Study Information	0065

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			CMC Investigational Plan	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Annual Report
Serial No.: 065

Protocol: S3B30004, S3BA2001, S3BA2002, S3BA2003, S3BA3001, S3BA3002, S3BA3003, S3BB1003, S3BB1011, S3BB2011
Comment: Period Covering: 05 August 1997 through 04 August 1998

10-Sep-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0066

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 066

Protocol: S3B20013, S3BA3002
Protocol with Investigator(s):
S3B30004 with:
Michael D Crowell, M.D.
S3BA3001 with:
Thomas J Chiambretti, D.O.
S3BA3003 with:
Lin Chang, M.D., Thomas J Chiambretti, D.O., Douglas A Drossman, M.D., Richard White, M.D.

14-Sep-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0067

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 067

Protocol with Amendment(s):
S3BA2002 with:
05
S3BA3001 with:
04

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
15-Sep-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0068

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 068

Protocol: S3BA3003
ADR: A0067942A

15-Sep-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0069

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Initial
Serial No.: 069

Protocol: S3BA3003
ADR: A0070295A

25-Sep-1998	Glaxo Wellcome Correspondence	General Correspondence	Clinical	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence

05-Oct-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0070

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 070

Protocol: S3BA3003
ADR: A0070295A

16-Oct-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0071

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Investigator Serial No.: 071 Protocol: S3BA3002 Protocol with Investigator(s): S3B20012 with: Philip O Katz, M.D. S3B30004 with: William Y Chey, M.D., Arthur Green, D.O. S3BA3003 with: Patricia Raymond, M.D.			
26-Oct-1998	Glaxo Wellcome Correspondence	Minutes of Meeting	FDA Conference	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: October 6, 1998 to Discuss the Quality of Life Program for Alosetron			
26-Oct-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0072
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 072 Protocol: S3BB3002 ADR: B0060594A			
05-Nov-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	 Investigator Add	0073
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 073 Protocol with Investigator(s):			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
S3BA1001 with: Benoit Girard, M.D.				
06-Nov-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0075
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 075			
Protocol: S3BB3002 ADR: B0060594A				
09-Nov-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add	0074
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Serial No.: 074			
Protocol with Investigator(s): S3B30006 with: Charles Franklin Barish, M.D., John W Beckman, M.D., D Eric Bolster, M.D., William Y Chey, M.D., John K Earl, M.D., Robert M Finlaw, M.D., Robert Holmes, M.D., Robert D Lerner, M.D., Donato Ricci, M.D., Stephen C Schindler, M.D.				
10-Nov-1998	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0076
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 076			
20-Nov-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0077
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 077			
Protocol with Amendment(s): S3BA3003 with: 05				
23-Nov-1998	Food and Drug Administration Telephone Conversation	General Teleconference	Other	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Other FDA request for submission of DDMAC Meeting (6 October 1998) Summary to IND General Discussion Regarding NDA Plans			
Commitment: Submit request for pre-NDA meeting Commitment Responsibility: Mark Baumgartner Commitment Due Date: 15-Jan-1999				
24-Nov-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0078
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 078			
Protocol: S3BA3001 ADR: A0070339A				
01-Dec-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical	0079
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 079			
Protocol with Amendment(s):				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
S3BA1004 with: 01 Protocol with Investigator(s): S3BA1004 with: Ronald Goldwater, M.D.				
04-Dec-1998	Glaxo Wellcome Correspondence	Minutes of Meeting	FDA Conference	0080
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: FDA Conference Serial No.: 080			
Comment: Quality of Life Program				
07-Dec-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol		0081
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Serial No.: 081			
Protocol with Report(s): S3B20015 with: RM1998/00464/00				
11-Dec-1998	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0082
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 082			
Protocol: S3BA3001 ADR: A0070339A				
15-Dec-1998	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0083
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 083			

Protocol: S3B20012, S3BA2002, S3BA3001, S3BA3002, S3BA3003
Protocol with Investigator(s):
S3B30004 with:
Michael T Draelos, M.D.
S3B30006 with:
Richard D. Baerg, M.D., Jim Bauer, M.D., William R. Berry, M.D., Jeffrey R Breiter, M.D., Michael F Elmore, M.D., Richard Fisher, M.D., Duane D Fitch, M.D., Larry I Gilderman, M.D., Stephen L Green, M.D., Arnold O Hopland, M.D., Bruce Jones, M.D., Richard A Krause, M.D., Steven Krumholz, M.D., Jake C Lennard, M.D., Frederick H Opper, M.D., Clinton D Polhamus, M.D., Sidney Rosenblatt, M.D., Herbert Rubin, M.D., David J Sales, M.D., Eugene Spiotta, M.D., Michael Stadiem, M.D., Kevin L Tack, M.D., Troy Alan Tyner, M.D., Barry D Winston, M.D., James D Wolosin, M.D.

21-Dec-1998	Glaxo Wellcome Correspondence	General Correspondence	Protocol	0084
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Protocol Serial No.: 084			

Protocol: S3BA3003

21-Dec-1998	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0085
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol, Clinical Serial No.: 085			

Protocol with Amendment(s):
S3BA1006 with:
01

08-Jan-1999	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0086
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 086			

Protocol: S3B20015

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
08-Jan-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Request Status Update			
13-Jan-1999	Food and Drug Administration Correspondence	Comment/Information Request	CMC	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Comment/Information Request: CMC			
13-Jan-1999	Food and Drug Administration Correspondence	Minutes of Meeting	FDA Conference	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: Discuss Health-Related Quality of Life Endpoints in Phase 3 Studies			
18-Jan-1999	Glaxo Wellcome Correspondence	General Correspondence	Meeting Request	0087
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Request for Pre-NDA Meeting Serial No.: 087			
21-Jan-1999	Glaxo Wellcome Correspondence	Minutes of Meeting	Pre-NDA Meeting	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Minutes of Meeting: Request for Clarification			
22-Jan-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0088

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Other 1572 Change	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 088

Protocol: S3BA3003
Protocol with Investigator(s):
S3B30006 with:
Hector D Allende, M.D., Scott D Bleser, D.O., Lawrence F Blob, M.D., Jacques R. Caldwell, M.D., Dale Collins, M.D., James L Conrad, M.D., Douglas D Dalke, M.D., Michael G DeLissio, M.D., Michael T Draelos, M.D., Margaret A. Drehobl, M.D., W. Travis Ellison, M.D., John E Ervin, M.D., James I Fidelholtz, M.D., David L Fried, M.D., Syam P Gaddam, M.D., Komaranahalli P Ganeshappa, M.D., Arthur Green, D.O., Michael R Grossman, M.D., William H Holderman, M.D., David S James, DO, R Bruce Johnson, M.D., John Andrew Kallianos, M.D., George Koval, M.D., Michael Kurtz, M.D., Edwin Larkai, M.D., Desmond Leddin, M.D., Michael S Levine, M.D., Thomas Liebermann, M.D., Thomas LoIudice, DO, Oscar Martinez, M.D., H. Charles Miller, M.D., Philip B Miner, M.D., William S Mullican, M.D., James Novick, M.D., Alan Plotner, M.D., Bennett H Plotnick, M.D., Joseph Reddy, M.D., Earl Glen Robbins, M.D., Michael Safdi, M.D., Ronald Schwarz, M.D., John Q Stauffer, M.D., Bruce E Stein, M.D., Robert E Tepper, M.D., James R Wagner, M.D., Gilbert Weisman, DO, Gerald D Wolfley, M.D., William C Wu, M.D.
S3BA3002 with:
Patrick Schow, M.D.

22-Jan-1999	Glaxo Wellcome Correspondence	General Correspondence	Other	0089

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence: Response to FDA Meeting Minutes
Serial No.: 089

26-Jan-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0090

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 090

Protocol with Amendment(s):
S3B30006 with:
01, 02, 03

27-Jan-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Memorandum			
29-Jan-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0091
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 091			
Protocol with Amendment(s): S3BA3001 with: 05 Protocol with Report(s): S3BA3001 with: RM1997/000534/05				
29-Jan-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0092
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 092			
Protocol: S3BA3003 ADR: A0067942A				
12-Feb-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Amendment: Other	Clinical Transfer of Obligations to Contract Research Organization	0093
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 093			
Protocol with Amendment(s):				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

S3B20015 with:
01
Comment: ICON Clinical Research, Inc. 115 East Park Drive, Suite 200, Brentwood, TN 37027

12-Feb-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0094

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Initial
Serial No.: 094

Protocol: S3BB3001
ADR: B0062540A

17-Feb-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add Other 1572 Change	0095

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Protocol Amendment: New Investigator, Investigator Add
Serial No.: 095

Protocol: S3BA3003
Protocol with Amendment(s):
S3B30006 with:
04
Protocol with Investigator(s):
S3B30006 with:
Charles K Bedard, M.D., Michael T Bennett, M.D., Georges Choueri, M.D., Fabio Cominelli, M.D., Paula A Hall, M.D., Rashid A Khairi, M.D., James C Kisicki, M.D., Ross A Kommor, M.D., Robert L Lindenberg, M.D., David G Mangels, M.D., Joseph L Nelson, M.D., Oscar Oandasan, M.D., Pierre Pare, M.D., Deepen Patel, M.D., J Mark Provenza, M.D., Thomas J Pulliam, M.D., Allen Rubin, M.D., Per Sangfelt, M.D., Charles J Sigmund, M.D., Tom Storskrubb, M.D., Paul F Whitsitt, M.D., Marc J Zuckerman, M.D.
S3BA3001 with:
John K DiBaise, M.D.

18-Feb-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0096

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Serial No.: 096			
	Protocol with Amendment(s): S3B20015 with: 02			
26-Feb-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0097
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 097			
	Protocol with Amendment(s): S3BA3003 with: 06			
03-Mar-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0098
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 098			
	Protocol: S3B20012, S3B30004 Protocol with Investigator(s): S3B30006 with: William Bennetts, M.D., Einar Bjornsson, M.D., Sudhir K Dutta, M.D., Marie Fellke, M.D., Oliver D Gilliam, M.D., M Scott Harris, M.D., Marc S Kaufman, M.D., S Jon Mason, M.D., Gunnar Midhagen, M.D., Lars Sidenvall, M.D., David R Silvers, M.D., Amit Kumar Srivastava, M.D., Richard White, M.D., Ellis E Williams, M.D.			
12-Mar-1999	Glaxo Wellcome Correspondence	General Correspondence	Meeting Agenda or Details	0099
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: Pre-NDA Meeting Background Package Serial No.: 099			
15-Mar-1999	Glaxo Wellcome Correspondence	Information Amendment: Clinical	Safety	0100

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Study Reports	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Information Amendment: Clinical
Serial No.: 100

Protocol with Report(s):
S3BA3001 with:
RM1998/00429/00
S3BA3002 with:
RM1998/00430/00

16-Mar-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0101

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 101

Protocol: S3BA1001, S3BA2002, S3BA3003
Protocol with Investigator(s):
S3B20015 with:
Scott D Bleser, D.O., Troy Alan Tyner, M.D.
S3B30006 with:
Ian Barrison, M.D., Paul J Lebovitz, M.D., Mark L Lloyd, M.D., Seymour Mishkin, M.D., Henry Nyhlin, M.D., Marybeth Spanarkel, M.D., Nigel Stace, M.D., John A Walker, M.D.

24-Mar-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Safety	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Memorandum: Safety

Protocol: S3BB3001
ADR: B0065097A

25-Mar-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Safety	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Memorandum: Safety

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol: S3BB3001 ADR: B0065097A				
26-Mar-1999	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Meeting Agenda or Details	General Teleconference	Meeting Agenda or Details	
29-Mar-1999	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 102	10-Day ADR Report	Initial	0102
Protocol: S3BB3001 ADR: B0065097A				
05-Apr-1999	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 103	10-Day ADR Report	Initial	0103
Protocol: S3BB3002 ADR: B0065267A				
13-Apr-1999	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Meeting Agenda or Details	General Teleconference	Meeting Agenda or Details	
15-Apr-1999	Glaxo Wellcome Trip Report IND 48,487; GR68755 Tablets (alosetron hydrochloride)	Type	Pre-NDA Meeting	

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Type: Pre-NDA Meeting			
16-Apr-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0105

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 105

Protocol: S3B30004, S3BA3003
Protocol with Investigator(s):
S3B20015 with:
Charles Franklin Barish, M.D., John W Beckman, M.D., Johnthan M. Bern, M.D., Milan Brandon, M.D., John K Earl, M.D., Duane D Fitch, M.D., David S James, DO, Bruce Jones, M.D., Richard A Krause, M.D., Daniel M Kruss, M.D., Edwin Larkai, M.D., Oscar Oandasan, M.D., Vinod Rustgi, M.D., Howard I. Schwartz, M.D., Eugene Spiotta, M.D., Gerald D Wolfley, M.D., James D Wolosin, M.D.
S3B30006 with:
Sydney Bass, M.D., Frederick M. Braunstein, M.D., Thomas Anthony Carr, M.D., Lin Chang, M.D., Loganathon Govender, M.D., H Freeman Harris, M.D., Antony Barnabas Hawthorne, M.D., Simon K Holgate, M.D., John M Inadomi, M.D., Bernard King, M.D., Alan Lane, M.D., Anna Maclean, M.D., Gordon V Ohning, M.D., Vinod Rustgi, M.D., Bruce E Stein, M.D., Thomas Andrew Sylwestowicz, M.D., David Troughton, M.D., Ian Wallace, M.D., D. E. Ward, M.D., Mike Watson, M.D., Craig W Wiesenhutter, M.D.

16-Apr-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0104

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 104

Protocol: S3BB3002
ADR: B0065267A

26-Apr-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0107

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0107

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Protocol: S3BA3003, S3BA3004
Protocol with Investigator(s):
S3B20015 with:
Ian Berkowitz, M.D., Luis Bujanda, M.D., William Y Chey, M.D., Michael T Draelos, M.D., Jack H Hall, M.D., Steven Krumholz, M.D., Thomas Liebermann, M.D., Oscar Martinez, M.D., Philip B Miner, M.D., Daniel J Pambianco, M.D., Vinod Rustgi, M.D., Shahriar S Safavi, M.D., Herbert Schneider, M.D., Ronald Schwarz, M.D., Bruce E Stein, M.D., Michael Strimling, M.D., Robert E Tepper, M.D.
S3B30006 with:
Gilbert O Barbezat, M.D., Karna Dev Bardhan, M.D., Adrian Darrah, M.D., Montserrat Forne, M.D., Robert K Hippert, D.O., P B Irwin, M.D., David A Johnson, M.D., Michael P Jones, M.D., Chris Kyle, M.B., B.Ch., Alan Robert McFarland, M.D., H P McGoldbrick, M.D.
S3BA3002 with:
David S Hodges, M.D.

26-Apr-1999 | Glaxo Wellcome Correspondence | 10-Day ADR Report | Follow-up | 0106

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 0106

Protocol: S3BB3001
ADR: B0065097A

26-Apr-1999 | Glaxo Wellcome FAX/E-mail | Response to FDA Request/Comment | Clinical

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Response to FDA Request/Comment: Clinical

Protocol: S3BA2001

27-Apr-1999 | Food and Drug Administration Correspondence | Comment/Information Request | Other

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Comment/Information Request

Comment: Clarification of Minutes from Oct 6, 1998 meeting.

12-May-1999 | Food and Drug Administration Correspondence | Minutes of Meeting | Pre-NDA Meeting

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Minutes of Meeting: Pre-NDA Meeting			
17-May-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0108

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0108

Protocol: S3BA3003
Protocol with Investigator(s):
S3B20015 with:
Charles K Bedard, M.D., Charles Noah Berstein, M.D., FRCP(C), Harold Bloch, M.D., Jacques R. Caldwell, M.D., Fernando Carballo, M.D., Robert M Finlaw, M.D., Stephen L Green, M.D., William H Holderman, M.D., George Koval, M.D., Mark Lamet, M.D., Robert D Lerner, M.D., Dennis C. McCluskey, M.D., Arturo Perez Mota, M.D., William S Mullican, M.D., Igor Prokopiw, M.D., Luis Rodrigo, M.D., John Philip Wright, M.D.
S3B30006 with:
Janusz Jankowski, M.D., Chester W Kessler, M.D., Steve Lillis, M.D.

20-May-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical Other	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Response to FDA Request/Comment: Draft of the Benefit and Risks and ISE
Serial No.:

25-May-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0109

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Protocol Amendment: Change in Protocol
Serial No.: 0109

Protocol: S3B30004, S3B30006, S3BA3003

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol with Amendment(s): S3B20013 with: 01 Protocol with Investigator(s): S3B20015 with: Thomas LoIudice, DO, James R Wagner, M.D. Protocol with Report(s): S3B20013 with: RM1998/00185/01				
25-May-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0110
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 0110			
Protocol: S3B30006 ADR: B0066851A				
27-May-1999	Glaxo Wellcome Correspondence	General Correspondence	BA/BE Clinical CMC Nonclinical	0111
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: FDA Response Requested FDA Pre-NDA Meeting Minutes: Request for Clarification Plans to Address FDA Comments and Requests Serial No.: 0111			
Protocol: S3BA2001, S3BB1004				
02-Jun-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical CMC Meeting Agenda or Details Nonclinical	
	IND 48,487; GR68755 Tablets (alosetron hydrochloride)			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Teleconference: Clinical, CMC, Meeting Agenda or Details, Nonclinical			
03-Jun-1999	Food and Drug Administration Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Status Update	General Teleconference	Status Update	
Comment: Response to FDA request for information				
09-Jun-1999	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Clinical, CMC, Nonclinical, Request Status Update	General Teleconference	Clinical CMC Nonclinical Request Status Update	
14-Jun-1999	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Clinical, CMC, Meeting Agenda or Details, Nonclinical	General Teleconference	Clinical CMC Meeting Agenda or Details Nonclinical	
15-Jun-1999	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0112	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0112

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Protocol: S3B30006, S3BA3003
Protocol with Investigator(s):
S3B20015 with:
Dale Collins, M.D., Enrique Dominguez, M.D., W. Travis Ellison, M.D., Per G Farup, M.D., Ulf Fjosne, M.D., Ole Hoie, M.D., E Walter Hood, M.D., Rokay Kamyar, M.D., Paul J Lebovitz, M.D., Michael S Levine, M.D., Jacob Louw, Professor, David A Peura, M.D., Michael Safdi, M.D., Asbjorn Stallemo, M.D., Roald Torp, M.D., John A Walker, M.D., Sigurd Wetterhus, M.D., Richard White, M.D.

17-Jun-1999	Food and Drug Administration Correspondence	Comment/Information Request	Clinical CMC Nonclinical	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Comment/Information Request: Clinical, CMC, Nonclinical

18-Jun-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Other	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Teleconference: Clinical, Other

Comment: Call to clarify the FDA fax of 17 June 1999; response to GWletter of 27 May 1999.

24-Jun-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0113

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0113

Protocol with Investigator(s):
S3B20015 with:
Roland William Bennetts, M.D., Michel Boivin, M.D., Michael Kurtz, M.D., Charles W Scowcroft, M.D., Arne W Wilskow, M.D.
S3B30006 with:
Gary E Poleynard, M.D.

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
24-Jun-1999	Glaxo Wellcome Telephone Conversation	Response to FDA Request/Comment	Clinical	

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Response to FDA Request/Comment: Clinical

07-Jul-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	 Investigator Add	0114

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Serial No.: 0114

Protocol with Investigator(s):
S3B10906 with:
Michael Camilleri, M.D.
Protocol with Report(s):
S3B10906 with:
NN1999/00052/00

12-Jul-1999	Glaxo Wellcome Correspondence	General Correspondence	Clinical Meeting Request	0115

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
General Correspondence: Clinical, Meeting Request
Serial No.: 0115

Protocol: S3BA3001, S3BA3003

14-Jul-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	Investigator Add Investigator Add	0116

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Serial No.: 0116

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
22-Jul-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0117

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0117

Investigator: Archambault, Andre, Beckwith, Jay G, Bursey, Ronald Ford, Drossman, Douglas A, Fidelholtz, James I, Scholz, David George, Winston, Barry D, Zanten, Sander Van

05-Aug-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0118

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0118

Protocol: S3B30004, S3B30006, S3BA3003
Protocol with Investigator(s):
S3B20015 with:
Alan Plotner, M.D.

11-Aug-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	 Investigator Add	0119

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Serial No.: 0119

Protocol with Investigator(s):
S3B30011 with:
Chester L. Fisher, Jr., M.D.

18-Aug-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Other 1572 Change	0120

IND 48,487; GR68755 Tablets (alosetron hydrochloride)

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Investigator Serial No.: 0120			
Protocol: S3B20015, S3BA3003				
19-Aug-1999	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0121
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0121			
01-Sep-1999	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0122
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0122			
08-Sep-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0123
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0123			

Protocol: S3B20015, S3B30006, S3BA3003
Protocol with Investigator(s):
S3B30011 with:
Lawrence K. Alwine, M.D., Marcelo A Barreiro, M.D., Charles I Biltz, M.D., Lee M Carter, M.D., Charles J Cattano, M.D., F.A.C.P., John J Champlin, M.D., Christopher M. Chappel, M.D., Park T Chittom, M.D., Frank N. Cole, M.D., Kathleen L Collins, M.D., William Thomas Garland, M.D., Nazim Jaffer, M.D., Richard B Jonas, M.D., Richard E Lassiter, M.D., Mel E Lucas, D.O., Michael A McAdoo, M.D., Jerry L Miller, M.D., Lanning R Newell, M.D., Gary E Poleynard, M.D., J Mark Provenza, M.D., Kenneth W Rioctor, M.D., Steven E Roberts, M.D., Michael A Rosemore, M.D., Eric S Solomon, M.D., Malcolm J. Sperling, M.D., Kenneth R. W. Warren, M.D., James L Williams II, M.D., Douglas Young, M.D.

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
14-Sep-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	 Investigator Add Transfer of Obligations to Contract Research Organization	0124

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0124

Protocol with Investigator(s):
S3B30012 with:
Marcelo A Barreiro, M.D.
Protocol with Report(s):
S3B30012 with:
RC1999/00003/00
Comment: IBAH, Four Valley Square, 512 Township Line Rd., Blue Bell, PA 19422

15-Sep-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0125

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 0125

Protocol: S3BB3001
ADR: B0062540A

15-Sep-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0126

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Initial
Serial No.: 0126

Protocol: S3BB3002
ADR: B0070392A

17-Sep-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add	0127

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0127			
Protocol with Investigator(s): S3B30011 with: Steven M Adkins, M.D., Louis V Antignano, M.D., Allan B Aven, M.D., Joan Ryder Benz, M.D., Eileen M Brady, M.D., Robert E. Broker, M.D., Robert G Cesarec, M.D., Adnan Dahdul, M.D., Mark I DeBruin, D.O., Ronald G DeGarmo, D.O., Hugh D Durrence, M.D., Ronald D Emkey, M.D., FACP, James T. Farrell, D.O., Edwin B Flanagan, D.O., Mark S. Fraley, D.O., Kathryn G Gilliland, M.D., David R Hassman, D.O., John A. Jernigan, M.D., John F Johanson, M.D., Neil M Kassman, M.D., Lionel Bernard Katchem, D.O., PC, Milton J Koch, M.D., Michael J McCartney, M.D., Jeffrey R Medoff, M.D., FACG, Paul Hooper Nichols, M.D., Larry R Popeil, M.D., FAAFP, Albert J Razzetti, M.D., Adisesha B Reddy, M.D., Mario Z Rosenberg, M.D., Valeria A Scott, M.D., William N Sokol, Jr., M.D., Randall R. Stoltz, M.D., Gregg A Valenzuela, M.D., Arthur S Waldbaum, M.D., Colin L Walker, M.D., Charles W White, Sr., M.D., Gregory J Wiener, M.D., Steven Wilson, M.D.			
17-Sep-1999	Glaxo Wellcome Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference	General Teleconference	Clinical CMC Nonclinical Protocol Request Status Update	
28-Sep-1999	Food and Drug Administration Telephone Conversation IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Teleconference: Status Update	General Teleconference	Status Update	
29-Sep-1999	Glaxo Wellcome Correspondence IND 48,487; GR68755 Tablets (alosetron hydrochloride)	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator	Clinical Investigator Add	0128

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Protocol Amendment: New Investigator Serial No.: 0128			

Protocol: S3B20023
Protocol with Amendment(s):
S3B20023 with:
01
Protocol with Investigator(s):
S3B20023 with:
R Bruce Johnson, M.D.

30-Sep-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0129
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 0129			

Protocol with Amendment(s):
S3B10906 with:
01
S3B20015 with:
03
S3B30006 with:
05
S3BA1006 with:
02
Protocol with Report(s):
S3B10906 with:
NN1999/00052/01
S3B20015 with:
RM1998/00464/03
S3B30006 with:
GM1998/00349/01
S3BA1006 with:
NN1998/00001/02

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
30-Sep-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0130

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 0130

Protocol: S3BB3002
ADR: B0070392A

01-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0131

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0131

Protocol with Investigator(s):
S3B30004 with:
William Y Chey, M.D.
S3B30006 with:
Arthur Green, D.O., Bruce Jones, M.D.
S3B30011 with:
Kevin Howard Ashby, M.D., Charles A Birbara, M.D., Mark David Blitstein, M.D., Michael L Bloom, M.D., Fred A Brosco, M.D., John A Brose, M.D., Charles J Cattano, M.D., F.A.C.P., Richard Charles Coalson, M.D., Teresa L Coats, M.D., William Randall Cox, M.D., William A Daniel, M.D., Robert A Davenport, M.D., Enrique Carlos M. De Castro, M.D., David W Dozer, M.D., John J Eck, M.D., Atilla Ertan, M.D., Robert A Feldman, M.D., Jeffrey D Feldstein, M.D., Scott D Fenske, M.D., Don S Fixler, M.D., Ronald A Ford, M.D., Marie Monique Forred, M.D., John D Gabriel, M.D., David B George, M.D., Harvey A Giller, M.D., Michael W Gorsky, M.D., Louis J Gringeri, M.D., Frances F Haas, M.D., David Harari, M.D., Robert Hardi, M.D., Richard E Hedrick, Jr., M.D., Timothy M Howard, M.D., Stephen L Ionna, M.D., Neil M Kassman, M.D., Ross A Kommor, M.D., William F Korcek, M.D., James A Krug, M.D., Mark Eliot Kutner, M.D., Daniel Henri Laury, M.D., Lawrence S Levinson, M.D., Robert Darryl Marks, M.D., George T Maughan, M.D., Frank Mazzone, M.D., Gregory M Mula, M.D., John D Nuschke, M.D., Ralph Steven Pulverman, D.O., Marina Raikhel, M.D., Robert B Rhoades, M.D., Scott P Sainburg, M.D., Barry Michael Schultz, M.D., Jerrold Lloyd Schwartz, M.D., William M Seger, M.D., Umedchandra K Shah, M.D., Joseph Neville Shepherd, Jr., M.D., Gerard V Siciliano, M.D., Ann L Silverman, M.D., James A Simon, M.D., J Christopher Stringer, M.D., Steven L Thomason, M.D., Michael U Todd, M.D., Monte E Troutman, D.O., Jonathan S Wechsler, D.O., L Michael Weiss, M.D., David J Wenzel, M.D., Barry D Winston, M.D., Robert J Ziltzer, M.D.
S3B30012 with:
Paula A Crenshaw, M.D., Todd J Hammer, M.D., Jeffrey R Herbst, M.D., Annette R Hull, M.D., Rajeev K Jain, M.D., Mohammad Nadeemullah, M.D., Kristine D Weiss, M.D.
S3BA3003 with:
Charles K Bedard, M.D., Roland William Bennetts, M.D., Philip C Bird, M.D., William H Holderman, M.D., David A Johnson, M.D., Chester W Kessler, M.D., Thomas LoIudice, DO, James McGill, M.D., Alan Plotner, M.D., Stephen C Schindler, M.D., Charles W Scrowcroft, M.D., Steven J Wegley, M.D., James D Wolosin, M.D.

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
01-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator	 Investigator Add	0132

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Serial No.: 0132

Protocol: S3B10935
Protocol with Investigator(s):
S3B10935 with:
Philip T Leese, M.D.

04-Oct-1999	Glaxo Wellcome Correspondence	Annual Report	Adverse Event Summary Changes to Investigator's Brochure Clinical Study Information CMC Investigational Plan Outstanding Regulatory Business	0133

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Annual Report
Serial No.: 0133

Protocol: S3B20012, S3B20013, S3B20015, S3B30004, S3B30006, S3BA1001, S3BA1002, S3BA1004, S3BA1006, S3BA2002, S3BA3001, S3BA3002, S3BA3003, S3BB2011
Comment: Period Covering: August 5, 1998 - August 4, 1999

08-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0134

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0134

Protocol with Investigator(s):
S3B20015 with:
Roland William Bennetts, M.D., Scott D Bleser, D.O., Richard A Krause, M.D., Michael Safdi, M.D., David George Scholz, M.D.
S3B30006 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Fabio Cominelli, M.D., James I Fidelholtz, M.D., Chester W Kessler, M.D., Richard A Krause, M.D., S Jon Mason, M.D., William S Mullican, M.D., David J Sales, M.D., Gerald D Wolfley, M.D.
S3B30011 with:
Jay L Adler, M.D., Ajit S Arora, M.D., Michael P Basista, M.D., Parth S Bharill, M.D., Frederick A Bieberdorf, M.D., Robert L Brannon, M.D., Paul Martin Craig, M.D., Robert A Davenport, M.D., Jeffrey J Dorociak, M.D.,Ph.D., R David Ferrera, M.D., Jeffrey J Glass, M.D., S.C., Carl Allen Goetsch, M.D., Stanley B Goldberg, M.D., Michael J Goldstein, M.D., Daniel E Gremillion, M.D., James R Hill, M.D., Reed Blanchard Hogan, II, M.D., Isaac Kalvaria, M.D., James R Kelly, M.D., M.B.A., David G Kohm, M.D., Elliot Joseph Kopp, M.D., Gilbert Ledesma, M.D., Stefan P Marcuard, M.D., Thomas E Melchione, M.D., James M Mertesdorf, M.D., Sam E Moussa, M.D., Diane M Normandin, M.D., Thomas Francis O'Meara, M.D., Robert L Pintozzi, M.D., Bryan C Pogue, M.D., James C Pollock, M.D., Charles Wilson Randall, M.D., Dennis A Ruff, M.D., Mark P Runde, M.D., Frederick N Shuler, M.D., G Scott Smith, M.D., Richard N Steller, M.D., Patricia A Stephenson, M.D., Joanna K Tan, M.D., John Jerome Upchurch, M.D., Vincent F Vacca, M.D., Steven I Wilkofsky, M.D., Lawrence D Wruble, M.D.
S3B30012 with:
Craig A Ennis, M.D., William F Erfling, M.D., John T Foss, M.D., R William Hilty, M.D., William D Koltun, M.D., Joseph V Marino, M.D., Gayle S Moyer, M.D., William A Spisak, M.D., G Wynne Stubbs, M.D., Eric N Zacharias, M.D.
S3BA3003 with:
Michael G DeLissio, M.D., Martin D Gelfand, M.D., Arthur Green, D.O., Dennis C. McCluskey, M.D., William S Mullican, M.D.

12-Oct-1999 | Glaxo Wellcome Correspondence | 10-Day ADR Report | Initial | 0135

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Initial
Serial No.: 0135

Protocol: S3B20015
ADR: A0102342A

15-Oct-1999 | Glaxo Wellcome Correspondence | Protocol Amendment: New Investigator | Investigator Add
Other 1572 Change | 0136

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0136

Protocol with Investigator(s):
S3B20023 with:
Michael T Bennett, M.D., Scott D Bleser, D.O., Milan Brandon, M.D., Michael E Brewer, Ph.D., M.D., Eugene J Burbige, M.D., Michael F Elmore, M.D., Syam P Gaddam, M.D., Martin I Golding, M.D., Michael R Grossman, M.D., Paula H Hall, M.D., E Walter Hood, M.D., David S James, DO, John J Jolley, M.D., James H Linne, M.D., Robert Darryl Marks, M.D., Philip B Miner, M.D., Daniel J Pambianco, M.D., David S Schulman, M.D., William R Stern, M.D.
S3B30006 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Vernon G.K. Hee, M.D.
S3B30011 with:
Larry A Adler, M.D., Roger C Anderson, M.D., Joel I Bessoff, M.D., William C Bray, M.D., David C Chua, M.D., Margaret A. Drehobl, M.D., Samuel W Flannagan, M.D., Ronald Fogel, M.D., Michael M Gaspari, M.D., David R Greenberg, D.O., Laurie S Haas, M.D., Marvin A Heuer, M.D., Scott Ingber, M.D., Hymie Kavin, M.D., Nicholas A Knight, M.D., Kevin K Koffel, M.D., Lynda Beth Milligan, M.D., Joseph P Moore, M.D., Gayle S Moyer, M.D., Joy Schechtman, D.O., G Scott Smith, M.D., Dale A Sundwall, M.D., FACOG, Richard A Truesdale, Jr., M.D., John C Turse, M.D., Michael D Van Norstrand, M.D., John M Wadleigh, D.O., Richard A Wright, M.D., Barbara K Zedler, M.D.
S3B30012 with:
Larry A Adler, M.D., Paul I Berkowitz, M.D., David D Campbell, M.D., Frank S Eder, M.D., John J Giannone, M.D., Gregory M Knopf, M.D., Robert H Levine, M.D., Daniel M Young, M.D.
S3BA3003 with:
Oscar Oandasan, M.D.

15-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	Investigator Add Transfer of Obligations to Contract Research Organization	0137

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0137

Protocol with Investigator(s):
S3B30013 with:
Scott D Bleser, D.O.
Protocol with Report(s):
S3B30013 with:
RM1999/00195/00
Comment: ICON Clinical Research, 115 East park Drive, Suite 200, Brentwood, TN 37027

20-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	Investigator Add Transfer of Obligations to Contract Research Organization	0138

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0138			
Protocol with Investigator(s): S3B10939 with: Philip T Leese, M.D. Protocol with Report(s): S3B10939 with: NN1999/00080/00 Comment: Quintiles, Inc., 1007 Slater Rd., Chelsea Place, Durham NC 27703				
22-Oct-1999	Glaxo Wellcome Correspondence	Information Amendment: Chemistry Manufacturing and Controls	CMC	0139
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Information Amendment: Chemistry Manufacturing and Controls, CMC Serial No.: 0139			
25-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	 Investigator Add Transfer of Obligations to Contract Research Organization	0140
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other, Transfer of Obligations to Contract Research Organization Serial No.: 0140			
Protocol: S3B10937 Protocol with Investigator(s): S3B10937 with: Philip T Leese, M.D. Protocol with Report(s): S3B10937 with:				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
NN1999/00078/00				
Comment: Quintiles, Inc., 1007 Slater Road, Chelsea Place, Durham, NC 27703				
26-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	Investigator Add Transfer of Obligations to Contract Research Organization	0141

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0141

Protocol: S3B10936
Protocol with Investigator(s):
S3B10936 with:
Philip T Leese, M.D.
Protocol with Report(s):
S3B10936 with:
NN1999/00077/00
Comment: Quintiles, Inc., 1007 Slater Road, Durham, NC 27703

28-Oct-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0142

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Follow-up
Serial No.: 0142

Protocol: S3B20015
ADR: A0102342A

29-Oct-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0143

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 0143

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol with Amendment(s):				
S3BA3003 with:				
07				
Protocol with Report(s):				
S3BA3003 with:				
RM1997/00540/07				
01-Nov-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0144
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 0144			
Protocol: S3BA3001				
ADR: A0070339A				
01-Nov-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0145
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 0145			
Protocol: S3BA3003				
ADR: A0067942A				
05-Nov-1999	Glaxo Wellcome Correspondence	General Correspondence	Other	0146
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) General Correspondence: PROPOSED PEDIATRIC STUDY REQUEST Serial No.: 0146			
Protocol: S3B10903, S3B10934, S3B30015, S3B30016, S3B30018, S3B30019				
11-Nov-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0147
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Follow-up Serial No.: 0147			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol: S3B20015 ADR: A0102342A				
12-Nov-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0148

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0148

Protocol with Investigator(s):
S3B20015 with:
William Y Chey, M.D., W. Travis Ellison, M.D., Paul J Lebovitz, M.D., Shahriar S Safavi, M.D.
S3B20023 with:
Hector D Allende, M.D., Clifford J Appel, M.D., Charles Franklin Barish, M.D., Mark David Blitstein, M.D., Elizabeth S Bray, M.D., Jeffrey R Breiter, M.D., Lawrence B Cohen, M.D., Michael G DeLissio, M.D., Thomas N Dewar, M.D., Ben J Dolin, M.D., John K Earl, M.D., Jeffrey P Fenyves, M.D., Fred C Fowler, M.D., Kevin T Geraci, M.D., FACP, Carl Allen Goetsch, M.D., Mark G Griffin, M.D., Robert K Hippert, D.O., Robert Holmes, M.D., R Bruce Johnson, M.D., Bruce Jones, M.D., Boris Kerzner, M.D., Chester W Kessler, M.D., Terry D. Klein, M.D., Ross A Kommor, M.D., Steven Krumholz, M.D., Michael Kurtz, M.D., Charles W Laudenbach, M.D., Jake C Lennard, M.D., Mark L Lloyd, M.D., Thomas LoIudice, DO, Gregory D Mackay, M.D., Douglas H Orchard, M.D., Ronald E Pruitt, M.D., Joseph Reddy, M.D., Harvey Resnick, M.D., Sidney Rosenblatt, M.D., Michael Safdi, M.D., David J Sales, M.D., Michael Johannes Schmalz, M.D., Colleen M Schmitt, M.D.MHS, Howard I. Schwartz, M.D., Ronald Schwarz, M.D., Robert E Tepper, M.D., Ellis E Williams, M.D., James D Wolosin, M.D.
S3B30006 with:
Karna Dev Bardhan, M.D., William R. Berry, M.D., Robert M Finlaw, M.D., Antony Barnabas Hawthorne, M.D., Anna Maclean, M.D., Stephen M Schindler, M.D., James R Wagner, M.D.
S3B30011 with:
Simmy S Bank, M.D., Parth S Bharill, M.D., John W Birk, M.D., William H Bobbitt,III, M.D., Alvan E. Fisher, M.D., Marie Monique Forred, M.D., Dale P McGinty, M.D., Harold G McNeil, D.O., Radman Mostaghim, M.D., Michael I Nissensohn, M.D., Thomas Rosenfield, M.D., Stuart M Topkis, D.O.
S3B30012 with:
Joseph W Baker, M.D., Brian Thomas Bock, D.O., David S Brandenburg, M.D., Shari Anne Brazinsky, M.D., C Don Bryant, M.D., Francesco Cabrera, M.D., James P Capo, Jr., M.D., Billy G Chacko, M.D., Murray H Cohen, D.O., Martin J Drost, M.D., David S Friedman, D.O., Glenn D Gafford, M.D., Timothy J Gardner, M.D., Harry I. Geisberg, M.D., Jeffrey G Geohas, M.D., Harold Guy, M.D., Duane J Henk, M.D., Marvin A Heuer, M.D., David N Holt, M.D., Kevin D Inwood, M.D., George Whitfield James, M.D., Paul F Kamitsuka, M.D., DTM & H, Rokay Kamyar, M.D., Joseph William Kittinger, III, M.D., FACP, Eric J Klein, M.D., Scott H Lieberman, M.D., William E Lyles, M.D., David M Maccini, M.D., Keith A Nichols, M.D., John P Pasquariello, Jr., M.D., R Walter Powell, M.D., Mark K Radbill, D.O., Michele Reynolds, M.D., Janelle A Rhyne, M.D., FACP, Bruce A Salzberg, M.D., Frederick W Schnure, M.D., Howard I. Schwartz, M.D., Michael E Schwartz, D.O., Randall J Severance, M.D., Dirk P Slaker, M.D., Martin L Throne, M.D., David M Turner, M.D., James C Whatley, M.D., Barry D Winston, M.D., Lawrence D Wruble, M.D., Gary D Yeoman, D.O., Frank A Zazueta, M.D.
S3B30013 with:
Hector D Allende, M.D., Clifford J Appel, M.D., Charles Franklin Barish, M.D., Jim Bauer, M.D., John W Beckman, M.D., Michael T Bennett, M.D., Milan Brandon, M.D., Elizabeth S

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Bray, M.D., Jeffrey R Breiter, M.D., Michael E Brewer, Ph.D., M.D., Eugene J Burbige, M.D., Lawrence B Cohen, M.D., Selwyn A Cohen, M.D., Michael T Draelos, M.D., Michael F Elmore, M.D., Jeffrey P Fenyves, M.D., Fred C Fowler, M.D., David Gabbaizadeh, M.D., Syam P Gaddam, M.D., Kevin T Geraci, M.D., FACP, Oliver D Gilliam, M.D., Mark G Griffin, M.D., Michael R Grossman, M.D., Paula A Hall, M.D., Curtis Scott Horn, M.D., Sima G Issen, M.D., David S James, DO, R Bruce Johnson, M.D., John J Jolley, M.D., Chester W Kessler, M.D., Steven Krumholz, M.D., Jake C Lennard, M.D., James H Linne, M.D., Robert Darryl Marks, M.D., Daniel J Pambianco, M.D., Sidney Rosenblatt, M.D., Michael Safdi, M.D., Stephen C Schindler, M.D., David S Schulman, M.D., David B Stanton, M.D., Ellis E Williams, M.D., James D Wolosin, M.D.
S3BA3003 with:
Jacques R. Caldwell, M.D., Charles L Colip, M.D., Raquel Croitoru, M.D., Robert M Finlaw, M.D., Michael R Grossman, M.D., Robert Holmes, M.D., George Koval, M.D., Linda P Murray, M.D., Jansi Prabakaran, M.D., Patricia Raymond, M.D., Mario Z Rosenberg, M.D., Douglas Schumacher, M.D., Ronald Schwarz, M.D., Richard A Wright, M.D.

18-Nov-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Clinical Transfer of Obligations to Contract Research Organization	0149

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Amendment: Other, Transfer of Obligations to Contract Research Organization
Protocol Amendment: Change in Protocol
Serial No.: 0149

Protocol with Investigator(s):
S3B10938 with:
Philip T Leese, M.D.

18-Nov-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator Amendment: Other	Investigator Add Change in Medical Monitor	0150

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0150

Protocol: S3B30013
Protocol with Investigator(s):
S3B20023 with:
Shane Agnew, M.D., FRCP(C), Michel Boivin, M.D., Uduma Kalu, M.D., M.Sc., FRCP, Edwin Larkai, M.D., Gaetano Morelli, M.D., FRCP, Alan Thomson, M.D., M.S.C., Ph.D.,
S3B30013 with:
Shane Agnew, M.D., FRCP(C), Michel Boivin, M.D., Uduma Kalu, M.D., M.Sc., FRCP, Edwin Larkai, M.D., Joseph Loutfi, M.D., Gaetano Morelli, M.D., FRCP

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Comment: Christine Marie Hunt, M.D., F.A.C.P.				
29-Nov-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0151

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0151

Protocol with Investigator(s):
S3B20015 with:
Ronald Schwarz, M.D., Richard White, M.D.
S3B20023 with:
Kevin Howard Ashby, M.D., J Luis Bautista, M.D., John W Beckman, M.D., Thomas D Bianchi, M.D., Steven K Brodie, M.D., Nicholas W Cirillo, D.O., Selwyn A Cohen, M.D., Rand F Compton, M.D., Gordon T Connor, M.D., W. Travis Ellison, M.D., Michael S Epstein, M.D., Gulchin A Ergun, M.D., Duane D Fitch, M.D., David L Fried, M.D., Gregory Fusilier, M.D., Oliver D Gilliam, M.D., William R Harlan, III, M.D., William H Holderman, M.D., Curtis Scott Horn, M.D., Spencer B Jones, M.D., Donald G Kaufman, M.D., Douglas W Kirtley, M.D., Jack A Klapper, M.D., Richard A Krause, M.D., Michael S Levine, M.D., Hari N Malik, M.D., David G Mangels, M.D., David J Morin, M.D., William J O'Toole, M.D., Jacob L Pinnas, M.D., Gary E Poleynard, M.D., Lance A Rudolph, M.D., Michael D Schiff, M.D., Charles J Sigmund, M.D., Thomas J Sobieski, III, M.D., David B Stanton, M.D., Bruce E Stein, M.D., Ira E Stein, M.D., James G Sullivan, M.D., William H Taub, M.D., John A Walker, M.D., Strick J Woods, M.D.
S3B30006 with:
Oliver D Gilliam, M.D., Vernon G.K. Hee, M.D., Steven Krumholz, M.D., William S Mullican, M.D.
S3B30011 with:
Parth S Bharill, M.D., Charles I Biltz, M.D., John A Brose, M.D., Lee M Carter, M.D., William Randall Cox, M.D., Ronald D Emkey, M.D., FACP, James R Hill, M.D., Timothy M Howard, M.D., Ross A Kommor, M.D., Gary E Poleynard, M.D., Larry R Popeil, M.D., FAAFP
S3B30012 with:
Malek H Al-Omary, M.D., Shari Anne Brazinsky, M.D., Hubert S Gaskin, III, M.D., Harold Guy, M.D., Randall T Huling, M.D., Harold Isenberg, M.D., Robert M Karns, M.D., David O Kim, M.D., William E Lyles, M.D., Thomas Francis O'Meara, M.D., Dennis Pangtay, M.D., Andres Patron, Marina Raikhel, M.D., Michael E Schwartz, D.O., Frank A Zazueta, M.D.
S3B30013 with:
Steven K Brodie, M.D., Nicholas W Cirillo, D.O., Michael G DeLissio, M.D., Thomas N Dewar, M.D., Ben J Dolin, M.D., Michael S Epstein, M.D., Gulchin A Ergun, M.D., Richard Fisher, M.D., Duane D Fitch, M.D., Ronald Fogel, M.D., Gregory Fusilier, M.D., Robert K Hippert, D.O., Jack A Klapper, M.D., Richard A Krause, M.D., Michael Kurtz, M.D., Paul J Lebovitz, M.D., Thomas LoIudice, DO, N Martin Lunde, M.D., Gregory D Mackay, M.D., David G Mangels, M.D., Philip B Miner, M.D., David J Morin, M.D., Joseph L Nelson, M.D., Douglas H Orchard, M.D., Peter M Pardoll, M.D., Jacob L Pinnas, M.D., Joseph Reddy, M.D., Harvey Resnick, M.D., Lance A Rudolph, M.D., Shahriar S Safavi, M.D., James A Sattler, M.D., Michael D Schiff, M.D., Michael Johannes Schmalz, M.D., Colleen M Schmitt, M.D.MHS, David Jay Schneiderman, M.D., FACS, Howard I. Schwartz, M.D., Ronald Schwarz, M.D., Ira E Stein, M.D., James G Sullivan, M.D., William H Taub, M.D., Robert E Tepper, M.D., Gerald D Wolfley, M.D., Strick J Woods, M.D.
S3BA3003 with:
Rokay Kamyar, M.D., Richard A Krause, M.D., Herbert Rubin, M.D., Craig W Wiesenhutter, M.D.

29-Nov-1999	Glaxo Wellcome Correspondence	Information Amendment: Chemistry	CMC	0152

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
		Manufacturing and Controls		
		Protocol Amendment: New Protocol	Investigator Add	
		Protocol Amendment: New Investigator		

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Information Amendment: Chemistry Manufacturing and Controls
Protocol Amendment: New Protocol: PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY
Protocol Amendment: New Investigator
Serial No.: 0152

Protocol with Investigator(s):
S3B10903 with:
Gregory L Kearns, Pharm.D.
S3B10934 with:
Gregory L Kearns, Pharm.D.
Protocol with Report(s):
S3B10903 with:
NN1999/00069/00
S3B10934 with:
NN1999/00070/00

01-Dec-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Amendment: Other	Transfer of Obligations to Contract Research Organization	0153

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0153

Protocol: S3B30020
Protocol with Report(s):
S3B30020 with:
RC1999/00013/00
Comment: Quintiles, Inc., 1007 Slater Rd., Chelsea Place, Durham, NC 27703

08-Dec-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0154

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0154

Protocol with Investigator(s):
S3B20023 with:
Paul E Brown, M.D., Sudhir K Dutta, M.D., Vernon G.K. Hee, M.D., John F Johanson, M.D., Bernard King, M.D., Desmond Leddin, M.D., Robert D Lerner, M.D., Scot Michael Lewey, D.O., N Martin Lunde, M.D., Gaetano Morelli, M.D., FRCP, William S Mullican, M.D., Peter M Pardoll, M.D., William Paterson, M.D., FRCP(C), Bennett H Plotnick, M.D., Marcia Prest, M.D., FRCP(C), Lee R Rocamora, M.D., Shahriar S Safavi, M.D., James A Sattler, M.D., Eugene Spiotta, M.D., Ellis E Williams, M.D., John A Winder, M.D., John D Zander, M.D., Marc J Zuckerman, M.D.
S3B30011 with:
Steven M Adkins, M.D., Kathleen L Collins, M.D.
S3B30012 with:
Richard D. Baerg, M.D., Dale M Carter, M.D., Robert John Koval, M.D., David Raul Munoz, M.D., Steven L Nack, M.D., Julio E Navarro, M.D.
S3B30013 with:
Mark Atin, FRCP(C), Jim Bauer, M.D., J Luis Bautista, M.D., Thomas D Bianchi, M.D., Mark David Blitstein, M.D., D Eric Bolster, M.D., Paul E Brown, M.D., David L Fried, M.D., Carl Allen Goetsch, M.D., John Sawyer Goff, M.D., William H Holderman, M.D., Adesh K Jain, M.D., Thomas K Judd, M.D., Boris Kerzner, M.D., Bernard King, M.D., Terry D. Klein, M.D., Steven Krumholz, M.D., Edwin Larkai, M.D., Ben George Lazarus, D.O., Desmond Leddin, M.D., Robert D Lerner, M.D., Michael S Levine, M.D., Robert L Lindenberg, M.D., Bryan L Magenheim, M.D., Dennis C. McCluskey, M.D., William J O'Toole, M.D., Naynesh Patel, M.D., William Paterson, M.D., FRCP(C), Alan Plotner, M.D., Marcia Prest, M.D., FRCP(C), Donato Ricci, M.D., Thomas J Sobieski, III, M.D., James D Torosis, M.D., Lawrence D Wruble, M.D., John D Zander, M.D., Robert M. Zuckerman, M.D.
S3BA3003 with:
Sudhir K Dutta, M.D., Charles D Hanshaw, M.D., David A Johnson, M.D., Linda P Murray, M.D., Thomas J Pulliam, M.D., Patrick Schow, M.D., M. Scott Touger, M.D.

09-Dec-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: Change in Protocol Amendment: Other	Clinical Transfer of Obligations to Contract Research Organization	0155

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol: PEDIATRIC PROTOCOLS SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY
Protocol Amendment: Change in Protocol
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0155

Protocol with Amendment(s):
S3B30012 with:
01

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol with Report(s): S3B30012 with: RC1999/00003/01 S3B30015 with: RM1999/00324/00 S3B30019 with: RM1999/00327/00 Comment: ICON Clinical Research, 1110 W. Lake Cood Road, Suite 220, Buffalo Grove, IL 60089				
15-Dec-1999	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0157
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 0157			
Protocol with Amendment(s): S3B30020 with: 01 Protocol with Report(s): S3B30020 with: RC1999/00013/01				
15-Dec-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up Initial	0156
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) 10-Day ADR Report: Initial Serial No.: 0156			
Protocol: S3B30011 ADR: A0107106A				
21-Dec-1999	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0158
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0158			

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Protocol with Investigator(s):
S3B20015 with:
James I Fidelholtz, M.D.
S3B20023 with:
M Angeli Adamczyk, M.D., Kevin Howard Ashby, M.D., Gary M Barton, M.D., Charles K Bedard, M.D., Chrystian Dallaire, M.D., FRCP, CSPQ, Ghhislain Devroede, M.D., MSc, Ph.D., Michael T Draelos, M.D., Ronald Fogel, M.D., Robert M Gannan, M.D., John Sawyer Goff, M.D., Paula A Hall, M.D., Adesh K Jain, M.D., Thomas K Judd, M.D., Ross A Kommor, M.D., Paul J Lebovitz, M.D., Robert L Lindenberg, M.D., Donald E Loew, M.D., Pierre Pare, M.D., Naynesh Patel, M.D., Frederick N Shuler, M.D., Richard White, M.D.
S3B30006 with:
David A Johnson, M.D., Robert L Lindenberg, M.D., Denis M McCarthy, M.D., David J Sales, M.D., Stephen C Schindler, M.D., Charles J Sigmund, M.D., Craig W Wiesenhutter, M.D.
S3B30011 with:
Allan B Aven, M.D., Margaret A. Drehobl, M.D., David R Hassman, D.O., Neil M Kassman, M.D., Gilbert Ledesma, M.D., Harold G McNeil, D.O., Jerry L Miller, M.D., Radman Mostaghim, M.D., Steven E Roberts, M.D., Richard A Truesdale, Jr., M.D., Jonathan S Wechsler, D.O., James L Williams II, M.D.
S3B30012 with:
Donald R Abrahm, M.D., Syed Sabahat Ali, M.D., Michael D Baldinger, M.D., Mark E Baxter, M.D., Benigno B Bobon, M.D., Francis X Burch, M.D., Nasim Golzar, M.D., Marvin A Heuer, M.D., Rokay Kamyar, M.D., Seth R Lewis, M.D., David Louis Limauro, M.D., Simon D Murray, M.D., Brian W Pugh, D.O., Charles Wilson Randall, M.D., J. David Schmitz, M.D.
S3B30013 with:
Kevin Howard Ashby, M.D., Jacques R. Caldwell, M.D., Rand F Compton, M.D., Gordon T Connor, M.D., Chrystian Dallaire, M.D., FRCP, CSPQ, Ghhislain Devroede, M.D., MSc, Ph.D., Sudhir K Dutta, M.D., W. Travis Ellison, M.D., Martin I Golding, M.D., William R Harlan, III, M.D., M Scott Harris, M.D., James R Herron, M.D., Robert Holmes, M.D., E Walter Hood, M.D., Donald G Kaufman, M.D., Marc S Kaufman, M.D., Edwin Larkai, M.D., Hari N Malik, M.D., David J Morin, M.D., William S Mullican, M.D., John E Pappas, M.D., Ronald E Pruitt, M.D., Lee R Rocamora, M.D., Bruce E Stein, M.D., Ira E Stein, M.D., William R Stern, M.D., John A Winder, M.D.
S3B30020 with:
Lawrence B Cohen, M.D., Samuel J Daniel, M.D., Matthew G Davis, M.D., Pankaj K Kashyap, M.D.
S3BA3003 with:
Eugene J Burbige, M.D., Oliver D Gilliam, M.D., Michael W Gorsky, M.D., Charles D Hanshaw, M.D., Chester W Kessler, M.D.

23-Dec-1999	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0159

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
10-Day ADR Report: Initial
Serial No.: 0159

Protocol: S3B30012
ADR: A0107932A

06-Jan-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0160

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0160

Protocol with Investigator(s):
S3B20015 with:
Robert M Finlaw, M.D.
S3B20023 with:
David Armstrong, M.D., FRCP(C), Jacques R. Caldwell, M.D., Georges Choueri, M.D., Steven C Harnack, M.D., David G Mangels, M.D., Amit Kumar Srivastava, M.D., William R Stern, M.D.
S3B30011 with:
Enrique Carlos M. De Castro, M.D., Mark I DeBruin, D.O., R David Ferrera, M.D., Edwin B Flanagan, D.O., Marie Monique Forred, M.D., Harvey A Giller, M.D., Robert Hardi, M.D., David R Hassman, D.O., Marvin A Heuer, M.D., Thomas E Melchione, M.D., Joseph P Moore, M.D., Gayle S Moyer, M.D., Gary E Poleynard, M.D., Steven E Roberts, M.D., David J Wenzel, M.D., Douglas Young, M.D.
S3B30012 with:
Shari Anne Brazinsky, M.D., Michael S Fedotin, M.D., Zafar Sheikh, M.D., Frank A Zazueta, M.D.
S3B30013 with:
M Angeli Adamczyk, M.D., David Armstrong, M.D., FRCP(C), Charles K Bedard, M.D., Georges Choueri, M.D., Robert M Gannan, M.D., George Koval, M.D., Dale P Murphy, M.D., Frederick H Opper, M.D., Pierre Pare, M.D., Richard Warren Tobin, M.D., John A Walker, M.D.
S3BA3003 with:
Thomas McDonald, M.D., Bruce E Stein, M.D., M. Scott Touger, M.D.

11-Jan-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0161

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Serial No.: 0161
IND 59,496; Alosetron Hydrochloride Oral Solution
Serial No.: 0002
10-Day ADR Report: Initial

Protocol: S3B30011
ADR: A0108355A

21-Jan-2000	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0162

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Serial No.: 0162

Protocol with Amendment(s):
S3B20023 with:
02
S3B30006 with:
06
S3B30013 with:
01
Protocol with Report(s):
S3B20023 with:
RM1999/00206/01
S3B30006 with:
RM1998/00353/06
S3B30013 with:
RM1999/00195/01

31-Jan-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0163

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0163

Protocol with Investigator(s):
S3B20015 with:
Jay G Beckwith, M.D., E Walter Hood, M.D., Troy Alan Tyner, M.D., Richard White, M.D.
S3B20023 with:
Mark Atin, FRCP(C), Brian Thomas Bock, D.O., Mark A Bonner, M.D., Fred C Fowler, M.D., Stanley B Goldberg, M.D., Marshall T Hale, M.D., Robert A Hammer, M.D., H Freeman Harris, M.D., M Scott Harris, M.D., Paul D King, M.D., George Koval, M.D., Daniel M Kruss, M.D., Louis R Lambiase, M.D., Ben George Lazarus, D.O., S Jon Mason, M.D., Dennis C. McCluskey, M.D., Anil Minocha, M.D., Vijay Narayen, M.D., Frederick H Opper, M.D., William M Pandak, M.D., Gary E Poleynard, M.D., Ronald Scott Powell, M.D., Stephen A Rafelson, M.D., Richard I Rothstein, M.D., William B Smith, M.D., Thomas Andrew Sylwestowicz, M.D., Kevin L Tack, M.D., Volkan O Taskin, M.D., Vincent F Vacca, M.D., Richard White, M.D., Lawrence D Wruble, M.D.
S3B30006 with:
Lin Chang, M.D., Robert M Finlaw, M.D., Syam P Gaddam, M.D., William H Holderman, M.D., H. Charles Miller, M.D.
S3B30012 with:
Thaddeus M Bort, M.D., Walter E Donnelly, M.D., Harold F Grooms, M.D., Steven J Gustaveson, M.D., Joseph P Hazen, M.D., Timothy J McCarren, M.D.
S3B30013 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Brian Thomas Bock, D.O., John K DiBaise, M.D., Marshall T Hale, M.D., Steven C Harnack, M.D., H Freeman Harris, M.D., Vernon G.K. Hee, M.D., Spencer B Jones, M.D., Christopher J Lahr, M.D., F.A.C.S., Scot Michael Lewey, D.O., Mark L Lloyd, M.D., Donald E Loew, M.D., Oscar Martinez, M.D., Igor Prokopiw, M.D., Stephen A Rafelson, M.D., Amit Kumar Srivastava, M.D., Kevin L Tack, M.D., Troy Alan Tyner, M.D., Craig W Wiesenhutter, M.D.
S3B30015 with:
Paul E Hyman, M.D., Gregory P Scagnelli, M.D., William N Sokol, Jr., M.D., Ramon Torres-Pinedo, M.D.
S3B30019 with:
Paul E Hyman, M.D., Gregory P Scagnelli, M.D., William N Sokol, M.D., Ramon Torres-Pinedo, M.D.
S3B30020 with:
Maxwell M Chait, M.D., Tawfik N Chami, M.D., Richard A Craven, M.D., Ritchard L Fishman, M.D., Michael R Gedeon, M.D., Frederick M Gessner, M.D., Jerome Howard, M.D., Brian K Hudes, M.D., John D Irvin, M.D., Anne L Macek, M.D., Jorge A Prieto, M.D., Thomas G Shetter, M.D., Mark Victor Shumeyko, M.D., Stanley R Walker, M.D.
S3BA3003 with:
Michael F Elmore, M.D.

03-Feb-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0164

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Serial No.: 0164
IND 59,496; Alosetron Hydrochloride Oral Solution
Serial No.: 0003
10-Day ADR Report: Initial

Protocol: S3BB3002
ADR: B0070503A

10-Feb-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0165

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0165

Protocol with Investigator(s):
S3B10934 with:
Jeffrey L Blumer, M.D.
S3B20023 with:
Ronald Ford Bursey, M.D., Donald Duerksen, M.D., FRCP(C), Carlo Fallone, M.D., CM, FRCP(C), David A Johnson, M.D., Benjamin Lasko, M.D., Elliot M Morris, M.D., William S Mullican, M.D., David Jay Schneiderman, M.D., FACS
S3B30012 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

P Frederick Duckworth, Jr., M.D., Robert Scott Kaufmann, M.D., FACP, Radha P Narayanan, M.D., Rakesh Prasad, M.D.
S3B30013 with:
Ronald Ford Bursey, M.D., Donald Duerksen, M.D., FRCP(C), Benjamin Lasko, M.D., Joseph Reddy, M.D., Thomas Andrew Sylwestowicz, M.D.
S3B30015 with:
Scot Michael Lewey, D.O.
S3B30019 with:
Scot Michael Lewey, D.O.
S3B30020 with:
Cyrus A Badii, M.D., Gary R Bodner, M.D., Richard W Brown, M.D., Ralph L Burke, M.D., Thomas J Byer, M.D., Charles J Cattano, M.D., F.A.C.P., Peter N Christie, D.O., David H.B. Cort, M.D., David M Felig, M.D., Daniel E Gremillion, M.D., Kirk D Jacobson, M.D., Fred A Levin, M.D., Rao V Movva, M.D., Morris A Pollock, M.D., John E Poulous, M.D., Myron L Rodos, D.O., Bavikatte N Shivakumar, M.D., Richard C Siler, M.D., Leonard B Weinstock, M.D., Robert A Weiss, M.D., Felice R Zwas, M.D.

21-Feb-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0166

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0166

Protocol with Investigator(s):
S3B20023 with:
Matthew Acampora, M.D., Sydney Bass, M.D., Gerald Bertiger, M.D., D Eric Bolster, M.D., Alan Cockeram, M.D., FRCP(C), John K DiBaise, M.D., James E Gardiner, M.D., John Sawyer Goff, M.D., James M Gordon, M.D., M Scott Harris, M.D., Christopher J Lahr, M.D., F.A.C.S., Benjamin F Lewis, M.D., Emeran A Mayer, M.D., Peter L Moses, M.D., Dale P Murphy, M.D., Bennett H Plotnick, M.D., Joseph Reddy, M.D., David S Schulman, M.D., Howard I. Schwartz, M.D., Reza Shaker, M.D., Kevin L Tack, M.D., Richard Warren Tobin, M.D., Troy Alan Tyner, M.D., Richard A Wright, M.D.
S3B30011 with:
Steven M Adkins, M.D., David W Dozer, M.D., John D Gabriel, M.D., John F Johanson, M.D., Gilbert Ledesma, M.D., Michael J McCartney, M.D., Albert J Razzetti, M.D., Steven Wilson, M.D.
S3B30012 with:
Malik N Baz, M.D.
S3B30013 with:
Matthew Acampora, M.D., Gary M Barton, M.D., Sydney Bass, M.D., Alan Cockeram, M.D., FRCP(C), John K Earl, M.D., Carlo Fallone, M.D., CM, FRCP(C), James E Gardiner, M.D., Daniel M Kruss, M.D., Ben George Lazarus, D.O., N Martin Lunde, M.D., Emeran A Mayer, M.D., Bennett H Plotnick, M.D., Ronald Scott Powell, M.D., Reza Shaker, M.D., William B Smith, M.D., Richard A Wright, M.D.
S3B30015 with:
Michael Cosgrove, M.D., Harry A Cynamon, M.D., Lars Danielson, M.D., G Kevin Donovan, M.D., Alejandro F Flores, M.D., Jan-Ake Hammersjo, M.D., Jeffrey S Hyams, M.D., Huw Ritchie Jenkins, M.D., Eva Lindberg, M.D., Josefa Martinez, M.D., Anthony R Otley, M.D. FRCPC, Richard L Sigmon, Jr., M.D., Lars Stenhammer, Assistant Professor
S3B30019 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

Harry A Cynamon, M.D., Lars Danielson, M.D., G Kevin Donovan, M.D., Alejandro F Flores, M.D., Jan-Ake Hammersjo, M.D., Jeffrey S Hyams, M.D., Eva Lindberg, M.D., Anthony R Otley, M.D. FRCPC, Richard L Sigmon, Jr., M.D., Lars Stenhammer, Assistant Professor
S3B30020 with:
William Anderson, M.D., Mohammad S Anwar, M.D., Manuel E Babaian, M.D., S Murthy Badiga, M.D., Robert C Barnes, M.D., Michael D Bender, M.D., Steven A Berley, D.O., David A Carron, M.D., Laura M Cho, M.D., Victor J Croglio, M.D., Mark DeFrancesco, M.D., Mark K Detweiler, M.D., David J Drewitz, M.D., Bryan N Feldman, D.O., Glenn S Freed, D.O., Stuart Friedman, M.D., William Lewis Gray, M.D., David M Gutman, M.D., Ruth A Hamad, M.D., Joseph Jue-Teng Hsu, M.D., John S Jackson, M.D., Thomas G Jenko, M.D., Steven C Kaiser, M.D., Mario D Kamionkowski, M.D., Robert W Keller, M.D., Niko I Keys, M.D., Ben George Lazarus, D.O., W Park McGehee, M.D., Adrian Meyer, M.D., Stephen H. Miller, M.D., Kumar Mukerjee, M.D., Richard M Pavelock, M.D., Gregory J Pleasants, M.D., Alan A Rosen, M.D., Joshua Beule Shipley, M.D., Lawrence B Stein, M.D., Werner A Studer, M.D., Sandra Tirado, M.D., Fei-Sen Yung, M.D.

24-Feb-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0167

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Serial No.: 0167
IND 59,496; Alosetron Hydrochloride Oral Solution
Serial No.: 0005
10-Day ADR Report: Follow-up

Protocol: S3B30011
ADR: A0108355A

25-Feb-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Protocol Protocol Amendment: New Investigator Amendment: Other	 Investigator Add Transfer of Obligations to Contract Research Organization	0168

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Protocol
Protocol Amendment: New Investigator
Amendment: Other, Transfer of Obligations to Contract Research Organization
Serial No.: 0168

Protocol: S3B40031
Protocol with Investigator(s):
S3B40031 with:
James T. Farrell, D.O.
Protocol with Report(s):
S3B40031 with:

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
RM2000/00022/00				
Comment: Kern McNeil International, Weston One, 1001 Winstead Drrive, Suite 530, Cary, NC 27513				
01-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0169

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0169

Protocol with Investigator(s):
S3B10934 with:
B. Ulysses Kwang Li, M.D.
S3B20015 with:
E Walter Hood, M.D., Charles W Scowcroft, M.D.
S3B20023 with:
Frederick M. Braunstein, M.D., Raquel Croitoru, M.D., E Walter Hood, M.D., David G Mangels, M.D., Emeran A Mayer, M.D.
S3B30011 with:
Ajit S Arora, M.D., William H Bobbitt,III, M.D., Kathleen L Collins, M.D., William Randall Cox, M.D., Paul Martin Craig, M.D., Michael J Goldstein, M.D., Stephen L Ionna, M.D., Jerry L Miller, M.D., Bryan C Pogue, M.D., Larry R Popeil, M.D., FAAFP, William N Sokol, Jr., M.D., Dale A Sundwall, M.D., FACOG, Arthur S Waldbaum, M.D.
S3B30012 with:
Francis X Burch, M.D., Robert B Nett, Jr., M.D., Barry D Winston, M.D.
S3B30013 with:
Frederick M. Braunstein, M.D., James M Gordon, M.D., Elliot M Morris, M.D., Mark Reichelderfer, M.D.
S3B30015 with:
Bisher Abdullah, M.D., Ramalingam Arumugam, M.D., Lawrence J Hak, M.D., Joseph R.A. Ignacio, M.D., Paul J Lebovitz, M.D., Dror Wasserman, M.D.
S3B30019 with:
Bisher Abdullah, M.D., Ramalingam Arumugam, M.D., Lawrence J Hak, M.D., Joseph R.A. Ignacio, M.D., Paul J Lebovitz, M.D., Dror Wasserman, M.D.
S3B30020 with:
Joseph M Alcorn, M.D., Peter Arcuri, D.O., Ph.D., Jody S Berner, M.D., R. Allen Blosser, M.D., Robert R Brinson, M.D., Dennis K Buth, M.D., LeRoy J Byrd, M.D., Mauricio H Caceres, M.D., Pundari K Chemitiganti, M.D., Gregory J Clark, M.D., Bruce C Corser, M.D., Gordon W Decker, M.D., Steven L Duckor, M.D., Jose M Duran, M.D., Ph.D., Todd D Eisner, M.D., Serhat Erzurum, M.D., Mitchell S Flaxman, M.D., Kenneth K Gheysar, M.D., Charles A Gonzalez, M.D., Paulino J Gonzalez, M.D., Glen L Gordon, M.D., FACP, FACIP, David W Gothard, M.D., Mark G Griffin, M.D., Samuel I Han, M.D., Stephen K Hasley, M.D., Al N Hawks, M.D., David S Hunter, M.D., Mark Jacobs, M.D., Franklin E Kasmin, M.D., David Y Kawashiri, M.D., Jeffrey K Klingenstein, M.D., Jay A Kravitz, M.D., M.P.H., Michael Z Kurtz, D.O, P. R. Lewin, M.D., David Lin, M.D., Manish Madan, M.D., Jeffrey R Medoff, M.D., FACG, Moussa Y Menasha, M.D., Moothedath A Menon, M.D., Anthony G Miccio, M.D., Peter J Molloy, M.D., Stephen J Morris, M.D., Amrit P.S. Narula, M.D., Tuan Trong Nguyen, M.D., Steven L Palley, M.D., Charles H Parker, Jr., M.D., James B Parsons, M.D., Anil C Patel, M.D., MBA, Tri Minh Pham, M.D., Steven L Saunders, M.D.FACP, Rajiv Shah, M.D., Suryakant M Shah, M.D., Alex Sherman, M.D., Manuel Sklar, M.D., William J Snape, Jr., M.D., Timothy J Spurling, M.D., Kenneth Robert Stringer, M.D., Robert A Strzinek, Ph.D., D.O., Kosuke Tokunaga, M.D., Charles T Tweel, M.D., Katheryne A Wagner, M.D., Carl G West, M.D., Louis J Wilson, M.D., Amir Wind, M.D., Barry D Winston,

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
M.D. S3BA3003 with: Paul J Lebovitz, M.D.				
03-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0170
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: Change in Protocol Serial No.: 0170			
Protocol with Amendment(s): S3B30020 with: 02 Protocol with Report(s): S3B30020 with: RC1999/00013/02				
06-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0171
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0171			
Protocol with Investigator(s): S3B20015 with: Philip B Miner, M.D. S3B20023 with: Michael T Draelos, M.D. S3B30006 with: Charles K Bedard, M.D., Richard Fisher, M.D., Steven Krumholz, M.D., John Q Stauffer, M.D. S3B30013 with: Steven C Harnack, M.D., Natarajan Ravendhran, M.D., Janet S Specter, M.D., William R Stern, M.D. S3B30020 with: John Abdulian, M.D., Steven J Alexander, M.D., Joseph P Ambrose, M.D., Damian H Augustyn, M.D., Dwight L Bailey, M.D., Alan R Bank, M.D., Gerald Bertiger, M.D., David J Black, M.D., Phillip L Bressman, M.D., Jack H Bumgardner, Jr., M.D., Shekhar K Challa, M.D., Brian D Clarke, M.D., Monika M Cohen, M.D., John M Cook, M.D., Tonya Davis-Spaulding, M.D., Thomas R Degregory, M.D., Atilla Ertan, M.D., Michael A Faber, M.D., Ira L Flax, M.D., Tim E Folse, M.D., Donald E Frein, M.D., Richard A Geisman, M.D., Fadi Ghanem, M.D., Richard D Gordon, M.D., David R Heiman, M.D., E Coy Irvin, Jr., M.D., Allan L Kurtz, D.O., Lyle D Kurtz, M.D., Michael J Lipson, M.D., Paul N Maton, M.D.,				

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
David K McDonald, M.D., Ralph D McKibbin, M.D., Daniel A Meline, M.D., P.C., Elliot Allen Meltzer, M.D., Bharat K Misra, M.D., Morry Moskovitz, M.D., Sam Moskovitz, M.D., Souheil Moussly, M.D., Mark A Nagrani, M.D., Ramalingeswara R Nimmagadda, M.D., Martin M Nosan, M.D., Raman M Patel, M.D., Crescenzo Pisano, M.D., Bernard J Powers, M.D., Robert A Prestiano, Jr., M.D., Jonathon D Rand, M.D., Adisesha B Reddy, M.D., Lucian C Rice, Jr., M.D., Angelo C Rizzo, D.O., Allen J Rosenbaum, M.D., Larry I Rubin, M.D., Havinder S Sahni, M.D., William B Salt, II, M.D., Jerrold Lloyd Schwartz, M.D., Balu B Shetty, M.D., H. Paul Singh, M.D., Whitney T Slade, M.D., Glenn R Slomin, D.O., Thomas B Smith, M.D., Jonathan S Staub, M.D., John B Sturgeon, M.D., Basil S Waldbaum, M.D., Joseph L Wang, M.D., William S Watkins, M.D., John T Watson, M.D., Henry T Wittenberg, Jr., D.O., Philip C Yee, M.D., Yuen S Yee, M.D.				
10-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator	Investigator Add Other 1572 Change	0172

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: New Investigator
Serial No.: 0172

Protocol with Investigator(s):
S3B30012 with:
R Walter Powell, M.D., Barbara K Zedler, M.D.
S3B30013 with:
Louis R Lambiase, M.D.
S3B30015 with:
Urban Mydral, M.D., Christopher John Taylor, Professor, Michael Thomson, M.D., Pedro Uruzzuno, M.D.
S3B30019 with:
Luz Cilleruelo, M.D., Urban Mydral, M.D., Pedro Uruzzuno, M.D.
S3B30020 with:
Waldo L Avello, M.D., Bruce D Beck, M.D., Samuel A Berkman, M.D., Howard L Bernie, M.D., Don R Bosse, M.D., Richard G Byrd, M.D., William D Chey, M.D., Joseph H Crumbliss, M.D., Orin L Davidson, III, M.D., David C Duncan, M.D., Komaranahalli P Ganeshappa, M.D., Michael R Greenberg, M.D., M.B.A, Robert D Gross, M.D., John Andrew Kallianos, M.D., Peter Shin Kay, M.D., Thomas C Kockinis, M.D., Michael J Lipson, M.D., Leslie J Nowitz, M.D., Prakash B Patel, M.D., Joseph LaRue Richter, M.D., Dallas M Shone, M.D., Richard M Sperling, M.D., Eliot H Zimbalist, M.D.

16-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: Change in Protocol	Clinical	0173

IND 48,487; GR68755 Tablets (alosetron hydrochloride)
Protocol Amendment: Change in Protocol
Serial No.: 0173

Protocol with Amendment(s):
S3B30012 with:
02

Application: IND 48487; GR68755 Tablets (alosetron hydrochloride)
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol with Report(s): S3B30012 with: RC1999/00003/02				
21-Mar-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator		0175
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Protocol Amendment: New Investigator Serial No.: 0175			
21-Mar-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0174
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0174 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0006 10-Day ADR Report: Initial			
Protocol: S3B20023 ADR: A0114615A				
22-Mar-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0176
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0176 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0007 10-Day ADR Report: Follow-up			
Protocol: S3B30011 ADR: A0107106A				

EXHIBIT 9F

Document Chronology / Due Diligence Logs for

NDA 21-107

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
24-Jun-1999	Glaxo Wellcome Correspondence	User Fee	Establishment With Clinical Data	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
User Fee: With Clinical Data

29-Jun-1999	Glaxo Wellcome Correspondence	Original Submission User Fee General Correspondence	 Establishment DMF Patent Information	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Original Submission
User Fee: Establishment
General Correspondence: DMF, Patent Information

Protocol: S3B20012, S3B20013, S3B20015, S3B30004, S3B30006, S3BA1006, S3BA2002, S3BB3001, S3BB3002
Protocol with Report(s):
AS01 with:
JJD/94/001
AS02 with:
JJD/94/002
AS03 with:
JJD/94/003
C92- 058 with:
GCP/92/058
C92-006 with:
GCP/92/006
C92-019 with:
GCP/92/019
C92-057 with:
GMH/92/057
C92-087 with:
GCP/92/087
C9359 with:

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
FNL/94/004				
C94014 with:				
GCP/95/048				
G91-019 with:				
GMH/91/051				
GHP8917 with:				
GMH/91/025				
GHP8923 with:				
GMH/89/024				
GHP8937 with:				
GMH/90/009				
GHP8938 with:				
GMH/90/004				
GHP8944 with:				
GPK/91/005				
GHP9005 with:				
GMH/90/012				
GHP9013 with:				
GPK/91/007				
GHP9016 with:				
GMH/91/007				
GHP9021 with:				
GMH/91/002				
GHP9027 with:				
GMH/91/015				
GPK9001 with:				
GPK/90/006				
GPK9002 with:				
GPK/90/008				
S3B101 with:				
UCP/91/014				
S3B102 with:				
UCP/92/019				
S3B201 with:				
UCP/93/009				
S3BA1001 with:				
NN1999/00011/00				
S3BA1002 with:				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
NN1999/00032/00				
S3BA1004 with:				
NN1999/00025/00				
S3BA2001 with:				
GM1997/00189/00, RM1997/00436/02				
S3BA2003 with:				
RM1997/00819/00				
S3BA3001 with:				
RM1998/00429/00				
S3BA3002 with:				
RM1998/00430/00				
S3BA3003 with:				
RM1998/00487/00				
S3BB1001 with:				
GM1997/00307/00				
S3BB1003 with:				
GM1998/00196/00				
S3BB1004 with:				
NN1996/00003/00				
S3BB1006 with:				
GM1999/00098/00				
S3BB1007 with:				
GM1997/00310/00				
S3BB1009 with:				
GM1999/00049/00				
S3BB1010 with:				
PM1999/00001/00				
S3BB1011 with:				
NN1998/00003/00				
S3BB2011 with:				
GM1998/00275/00				
S3BH01 with:				
GGN/93/010				
S3BH02 with:				
GGN/93/011				
S3BH03 with:				
GGN/93/012				
S3BH04 with:				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #

GGN/93/013
S3BH05 with:
GGN/94/020
S3BH06 with:
GM1998/00287/00
S3BH08 with:
FNL/94/005
S3BP12 with:
GGN/94/022
Report: NME/94/030, SR1999/00022/00, SR1999/00023/00, SR1999/00029/00, WBP/89/046, WBP/89/060, WBP/89/062, WBP/89/071, WBP/89/097, WBP/89/100, WBP/89/101, WBP/90/041, WBP/90/052, WBP/90/055, WBP/90/056, WBP/90/057, WBP/90/062, WBP/90/063, WBP/90/069, WBP/90/073, WBP/90/097, WBP/90/099, WBP/91/002, WBP/91/008, WBP/91/017, WBP/91/041, WBP/91/044, WBP/91/045, WBP/91/046, WBP/91/047, WBP/91/098, WBP/91/099, WBP/91/105, WBP/91/108, WBP/92/011, WBP/92/021, WBP/92/037, WBP/92/088, WBP/92/129, WBP/93/013, WBP/93/019, WBP/93/020, WBP/93/029, WBP/94/012, WBP/94/037, WBP/95/042, WBP/95/048, WD1998/00003/00, WD1998/00191/00, WD1998/00330/00, WD1998/00402/00, WD1999/00113/00, WGP/93/021, WNP/89/056, WNP/89/057, WNP/89/069, WNP/90/004, WNP/90/005, WNP/90/006, WNP/90/007, WNP/90/008, WNP/92/060, WPT/88/069, WPT/89/056, WPT/89/103, WPT/89/152, WPT/89/166, WPT/89/188, WPT/89/202, WPT/89/211, WPT/89/214, WPT/89/218, WPT/89/237, WPT/89/242, WPT/89/244, WPT/89/247, WPT/89/249, WPT/89/250, WPT/89/271, WPT/89/282, WPT/89/328, WPT/89/330, WPT/90/014, WPT/90/131, WPT/90/161, WPT/90/163, WPT/90/164, WPT/90/188, WPT/90/229, WPT/90/302, WPT/90/304, WPT/90/335, WPT/91/002, WPT/91/012, WPT/91/024, WPT/91/058, WPT/91/164, WPT/91/409, WPT/92/025, WPT/92/095, WPT/92/325, WPT/93/134, WPT/93/360, WPT/93/503, WPT/95/148
Comment: Patent No.: 5,360,900 Ex Date: 2 Feb 10

29-Jun-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Response to FDA Request/Comment: Clinical

Protocol: S3BA1006, S3BA2001, S3BA2002, S3BA3001, S3BA3002, S3BA3003, S3BB1002, S3BP12
Protocol with Report(s):
AS01 with:
JJD/94/001
C92-006 with:
GCP/92/006
C92-019 with:
GCP/92/019
C92-057 with:
GCP/92/057
C9359 with:
FNL/94/004
C94014 with:

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
GCP/95/048				
G91-019 with:				
GMH/91/051				
GHP8917 with:				
GMH/91/025				
GHP8923 with:				
GMH/89/024				
GHP8937 with:				
GMH/90/009				
GHP8938 with:				
GMH/90/004				
GHP9005 with:				
GMH/90/012				
GHP9016 with:				
GMH/91/007				
GHP9027 with:				
GMH/91/015				
S3B101 with:				
UCP/91/014				
S3BA1001 with:				
NN1998/00093/00				
S3BA1002 with:				
NN1999/00032/00				
S3BA2003 with:				
RM1998/00819/00				
S3BB1001 with:				
GM1997/00307/00				
S3BB1003 with:				
GM1998/00196/00				
S3BB1006 with:				
GM1999/00098/00				
S3BB1007 with:				
GM1997/00310/00				
S3BB1009 with:				
GM1999/00049/00				
S3BB2011 with:				
GM1998/00275/00				
S3BH01 with:				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
GGN/93/010 S3BH02 with: GGN/93/011 S3BH03 with: GGN/93/012 S3BH04 with: GGN/93/013 S3BH05 with: GGN/94/020 S3BH06 with: GM1998/00287/00 S3BH08 with: FNL/94/005				
06-Jul-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other - NDA Administrative Issues	General Teleconference	Other	
09-Jul-1999	Food and Drug Administration Correspondence NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Acknowledgement: Receipt of NDA	Acknowledgement	060-Day Review Extension Other	
09-Jul-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other, Safety	General Teleconference	Other Safety	
13-Jul-1999	Food and Drug Administration Telephone	General Teleconference	Status Update	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Conversation NDA 21-036; RELENZA® (zanamivir for inhalation) General Teleconference: Status Update NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update NDA 21-077; ADVAIR™ DISKUS® (salmeterol/fluticasone propionate inhalation powder) 100 mcg, 250 mcg and 500 mcg General Teleconference: Other, Status Update			
27-Jul-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference	General Teleconference	Status Update	
02-Aug-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: , BA/BE, Clinical, CMC, Advisory Committee Meeting	Response to FDA Request/Comment	Advisory Committee Meeting BA/BE Clinical CMC	
05-Aug-1999	Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request	Response to FDA Request/Comment	BA/BE Other	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
05-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	BA/BE Clinical CMC DMF Electronic Format Other Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: BA/BE, Clinical, CMC, DMF, Electronic Format, Other, Statistical			
06-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC			
09-Aug-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Other - SAS Dataset Question			
Protocol: S3BA3001, S3BA3002				
09-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Statistical			
Protocol: S3BB1004 Commitment: Amendment to correct PK Summary (food effects study S3BB1004 Commitment Responsibility: K Kock/ M Baumgartner				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Electronic Format	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Comment/Information Request: Electronic Format

Protocol: S3BA3001, S3BA3002
Commitment: Amend the NDA to include the missing pages
Commitment Responsibility: M Baumgartner
Commitment Due Date: 13-Aug-1999

10-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical Other	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Response to FDA Request/Comment: Clinical

Comment: Electronic CRF's

10-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Electronic Format	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Comment/Information Request: Electronic Format

Protocol: S3BA3001, S3BA3002

11-Aug-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical CMC Meeting Request Other	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
General Teleconference: Clinical, CMC, Meeting Request, Other

Protocol: S3BA3001, S3BA3002
Commitment: Provide location within the application of C of As

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Commitment Responsibility: M Baumgartner Commitment Due Date: 12-Aug-1999				
11-Aug-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Statistical Reviewer Questions Regarding Datasets	Comment/Information Request	Statistical	
11-Aug-1999	Food and Drug Administration FAX/E-mail NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical	Comment/Information Request	Clinical	
13-Aug-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: CMC	Response to FDA Request/Comment	CMC	
17-Aug-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, CMC, Nonclinical	Comment/Information Request	Clinical CMC Nonclinical	
18-Aug-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Nonclinical: Datasets for oncogenicity studies	General Teleconference	Nonclinical	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Commitment: Submit desk copies of NDA volumes 1.10 through 1.15 and 1.24 through 1.29 Commitment Responsibility: M Baumgartner				
19-Aug-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other: Pharm/Tox (datasets for oncogenicity studies)			
19-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical DMF Electronic Format Safety	
		General Teleconference	Meeting Request	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, DMF, Electronic Format, Safety General Teleconference: Meeting Request			
Protocol: S3BA2001, S3BA3003, S3BP12				
20-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA2001, S3BP12				
23-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical			
Protocol: S3BA3001, S3BA3002				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-Aug-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Status Update			
23-Aug-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical			
23-Aug-1999	Food and Drug Administration FAX/E-mail	Comment/Information Request	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Statistical			
23-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	BA/BE Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment			
24-Aug-1999	Glaxo Wellcome Correspondence	General Correspondence	Meeting Request	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Meeting Request			
24-Aug-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Meeting Request	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Request			
24-Aug-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Meeting Agenda or Details Other Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Other, Status Update			
24-Aug-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Statistical			
25-Aug-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Nonclinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Nonclinical			
Report: D22693, DGRP1015, G22691, SR1999/00073/00				
25-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Nonclinical Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Cardiac Safety Information			
Protocol: S3B10932 Commitment: Timeline evaluation for the deliverables described above. Commitment Responsibility: M Baumgartner				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
25-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Other			
25-Aug-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Nonclinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Nonclinical			
26-Aug-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Other: DSI Information			
Comment: Copy of BIMO cover letter and TOC.				
26-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	BA/BE Clinical CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: BA/BE, Clinical, CMC			
27-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA3003				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
30-Aug-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Nonclinical			
30-Aug-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical CMC Efficacy Labeling Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Request Status Update			
31-Aug-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Nonclinical, Plans for Safety Update, Other: Pending Meeting Request			
01-Sep-1999	Glaxo Wellcome Correspondence	General Correspondence	CMC DMF	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: CMC, DMF			
02-Sep-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Meeting Agenda or Details Other	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Status Update	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
General Teleconference: Request Replacement for CRF PDF File; Status Update on Meeting Request and Question Responses

02-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical Other	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Response to FDA Request/Comment: Clinical, Other

Comment: Replacement .pdf formatted CRF tape.

03-Sep-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Nonclinical	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Amendment to Pending Application: Nonclinical

Report: WD1999/00381/00

07-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Comment/Information Request: Other: DSI Request

Protocol with Investigator(s):
S3BA3001 with:
Lin Chang, M.D., Oscar Oandasan, M.D., Michael Safdi, M.D.
S3BA3002 with:
Scott D Bleser, D.O., Rokay Kamyar, M.D., James R Wagner, M.D.

08-Sep-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Nonclinical Other	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Teleconference: Other: DSI Request			
Protocol with Investigator(s): S3BA3001 with: Lin Chang, M.D., Oscar Oandasan, M.D., Michael Safdi, M.D. S3BA3002 with: Scott D Bleser, D.O., Rokay Kamyar, M.D., James R Wagner, M.D.				
08-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Materials Requested for DSI Audits of Clinical Sites			
09-Sep-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical, Other (DSI Request)			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12				
10-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	BA/BE CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: BA/BE, CMC			
Report: UCP/92/026				
10-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Nonclinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Nonclinical			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical			
Protocol: S3BA3001 Commitment: Desk copy of 1.189 Commitment Responsibility: A Calisto Commitment Due Date: 10-Sep-1999				
13-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: GHP8923, GHP8938, GHP9005, GHP9013, GPK9001, S3B101, S3B102, S3BA1001				
14-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA3001, S3BA3002				
14-Sep-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, Request Status Update			
14-Sep-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Teleconference: Advisory Committee Meeting, Meeting Agenda or Details			
14-Sep-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Status Update Comment/Information Request: Nonclinical	General Teleconference	Meeting Agenda or Details Status Update Nonclinical	
14-Sep-1999	Glaxo Wellcome Correspondence NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical	Response to FDA Request/Comment	Clinical	
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12				
15-Sep-1999	Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: BA/BE	Response to FDA Request/Comment	BA/BE	
15-Sep-1999	Glaxo Wellcome Correspondence NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical	Response to FDA Request/Comment	Clinical	
Protocol: S3BA2001, S3BA3001, S3BA3002 Protocol with Report(s): S3B10932 with: NN1999/00059/00				

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
15-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Comment/Information Request: Clinical

Protocol: S3BA2001, S3BA3001, S3BA3002
Commitment: Submit requested records on patients
Commitment Responsibility: M Baumgartner

17-Sep-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Nonclinical	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Amendment to Pending Application: Nonclinical
Response to FDA Request/Comment: Nonclinical

Report: WD1999/00383/00, WD1999/00412/00

20-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Response to FDA Request/Comment: Clinical

Protocol: S3BA3002

20-Sep-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
General Teleconference: Advisory Committee Meeting

21-Sep-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	BA/BE	

NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Response to FDA Request/Comment: BA/BE
Correction to Previously Submitted Information: BA/BE

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
21-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Meeting details, submission status			
Protocol: S3B10932, S3BA3001, S3BA3003				
21-Sep-1999	Glaxo Wellcome Correspondence	General Correspondence	Advertising/Promotion	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Request for Comments on Proposed Product Logo			
22-Sep-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	CMC Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: CMC, Labeling			
22-Sep-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: CMC			
22-Sep-1999	Glaxo Wellcome Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: CMC Field Copy			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
23-Sep-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Nonclinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Nonclinical			
23-Sep-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Nonclinical, Other			
24-Sep-1999	Glaxo Wellcome Correspondence	120-Day Safety Update	Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets 90-Day Safety Update			
Protocol with Report(s): S3BA3003 with: RM1999/00344/00				
27-Sep-1999	Glaxo Wellcome Telephone Conversation	Response to FDA Request/Comment	Nonclinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Nonclinical			
28-Sep-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol: S3BA3001, S3BA3002				
29-Sep-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details			
29-Sep-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Meeting Agenda or Details Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details, Other			
30-Sep-1999	Glaxo Wellcome Correspondence	General Correspondence	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Meeting Details			
01-Oct-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting			
01-Oct-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
05-Oct-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details			
05-Oct-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Efficacy Meeting Agenda or Details Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Meeting Agenda or Details			
06-Oct-1999	Glaxo Wellcome Trip Report	Type	090-Day Conference	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Type: 090-Day Conference			
12-Oct-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting			
13-Oct-1999	Food and Drug Administration FAX/E-mail	Comment/Information Request	Clinical Efficacy Labeling Other Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Comment/Information Request: Other			
Protocol: S3BA3001, S3BA3002				
13-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Statistical			
Protocol: S3BA3001, S3BA3002				
14-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Electronic Format Other Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Review of Meeting Summary			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12				
15-Oct-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12				
15-Oct-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA2001, S3BA3001, S3BA3002				
21-Oct-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Other	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Critical Data Format			
21-Oct-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling Other Safety Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other: Status update			
22-Oct-1999	Food and Drug Administration FAX/E-mail	Comment/Information Request	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC			
22-Oct-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update			
22-Oct-1999	Food and Drug Administration Correspondence	Comment/Information Request	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC			
25-Oct-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Labeling Nonclinical Statistical	
		General Correspondence	Meeting Request	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment Summary of Meeting Discussion Topics and Outcomes Revised Draft Labeling Request for Teleconference			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BA3003, S3BP12				
25-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Advisory Committee Preparations			
26-Oct-1999	Food and Drug Administration FAX/E-mail	Comment/Information Request	CMC Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC, Other			
26-Oct-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Other			
26-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical			
27-Oct-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA3001, S3BA3002, S3BA3003				
27-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	CMC Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC, Other: Status Update			
27-Oct-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting			
27-Oct-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Information			
27-Oct-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Advisory Committee Meeting	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting			
28-Oct-1999	Glaxo Wellcome Correspondence	General Correspondence	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence Advisory Committee Meeting Briefing Document			
28-Oct-1999	Glaxo Wellcome Correspondence	General Correspondence	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Advisory Committee Meeting Briefing Document			
28-Oct-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Statistical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Statistical			
28-Oct-1999	Food and Drug Administration Correspondence	Comment/Information Request	Advertising/Promotion	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Advertising/Promotion			
MACMIS: 8307				
29-Oct-1999	Glaxo Wellcome Correspondence	General Correspondence	Clinical Other	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: PROPOSED PEDIATRIC STUDY REQUEST			
Protocol: S3B10903, S3B10934, S3B30015, S3B30016				
02-Nov-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: CMC			
02-Nov-1999	Glaxo Wellcome Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: CMC Field Copy			
03-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting			
04-Nov-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment General Memorandum	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting General Memorandum: Meeting Agenda or Details			
04-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Clinical	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Labeling Meeting Agenda or Details Meeting Request Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, Clinical, Labeling, Meeting Agenda or Details, Meeting Request, Request Status Update			
05-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other: DSI			
05-Nov-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting			
05-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, CMC			
05-Nov-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Advisory Committee Meeting, Meeting Agenda or Details			

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
09-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Other			
09-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting CMC Efficacy Meeting Agenda or Details Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, Request Status Update			
10-Nov-1999	Glaxo Wellcome Correspondence	General Correspondence	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Request for Partial Waiver and Deferral of Pediatric Studies			
Protocol: S3B10903, S3B10934, S3B30015, S3B30016, S3B30018, S3B30019				
10-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details			
10-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Request Status Update	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting, Request Status Update			
10-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details			
10-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Advisory Committee Meeting Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Advisory Committee Meeting			
12-Nov-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical			
Protocol: S3B30011				
12-Nov-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical			
Protocol: S3B30011				
12-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical CMC Safety	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Safety			
12-Nov-1999	Glaxo Wellcome Correspondence	General Correspondence	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Clinical			
Protocol: S3B30011				
15-Nov-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting			
15-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Advisory Committee Plans			
15-Nov-1999	Food and Drug Administration FAX/E-mail	General Memorandum	Meeting Agenda or Details	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Meeting Agenda or Details			
Protocol: S3BA3001, S3BA3002				
15-Nov-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Advisory Committee Meeting	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Advisory Committee Meeting			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
18-Nov-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Pathology Results			
18-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other			
19-Nov-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Clinical			
Protocol: S3B30011, S3BA2001, S3BA3002				
19-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Safety			
19-Nov-1999	Glaxo Wellcome Trip Report	Topic	Clinical Labeling Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Topic: Clinical, Labeling, Safety			
23-Nov-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical	Comment/Information Request	Clinical	
Protocol: S3BA3001, S3BA3002				
23-Nov-1999	Glaxo Wellcome Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical	General Teleconference	Clinical	
Commitment: Correct the administrative record (information previous submitted Oct 25, 1999) Commitment Responsibility: M Baumgartner				
23-Nov-1999	Food and Drug Administration Telephone Conversation NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Status update	Comment/Information Request	Clinical Other	
29-Nov-1999	Glaxo Wellcome FAX/E-mail NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical	Response to FDA Request/Comment	Clinical	
Protocol with Report(s): S3BA3003 with: RM1999/00344/00				
29-Nov-1999	Food and Drug Administration Telephone	Comment/Information Request	Clinical	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Conversation		CMC Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, CMC, Labeling			
29-Nov-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Other: Status Update			
30-Nov-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Labeling			
30-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical			
30-Nov-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
30-Nov-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Labeling Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Labeling, Safety			
01-Dec-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Clinical (Correction to previously submitted information)			
Protocol: S3BA3001				
01-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical (Correction to Previously Submitted Information)			
02-Dec-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Other Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other-Notification of Extension of the Review Clock, Labeling Activities, Status Update			
06-Dec-1999	Glaxo Wellcome Correspondence	Amendment to Pending Application	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Amendment to Pending Application: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
06-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			
06-Dec-1999	Glaxo Wellcome Correspondence	General Correspondence	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Labeling			
07-Dec-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3B30011, S3BA3001, S3BA3002, S3BA3003				
09-Dec-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Request Status Update Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Request Status Update, Safety			
10-Dec-1999	Food and Drug Administration Correspondence	Acknowledgement	090-Day Review Extension	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Acknowledgement: 090-Day Review Extension			

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
13-Dec-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA2001, S3BA3001, S3BA3002, S3BP12				
13-Dec-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling Request Status Update Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling, Request Status Update, Safety			
13-Dec-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Labeling			
14-Dec-1999	Glaxo Wellcome Correspondence	General Correspondence	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: Clinical			
Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032				
14-Dec-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Request Status Update			

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
15-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical, Labeling			
Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032				
15-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical			
Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032				
15-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Clinical			
Protocol: S3B20015, S3B20023, S3B30006, S3B30011, S3B30012, S3B30013, S3B30015, S3B30016, S3B30017, S3B30018, S3B30019, S3B30020, S3B30025, S3B40031, S3B40032				
16-Dec-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			
16-Dec-1999	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
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Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
17-Dec-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Labeling Other Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Labeling, Other, Safety			
17-Dec-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update: Labeling			
20-Dec-1999	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update: NDA Review, Labeling, Post Marketing Study Request			
21-Dec-1999	Food and Drug Administration Correspondence	Comment/Information Request	Clinical Efficacy Other Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Phase IV Commitments			
21-Dec-1999	Food and Drug Administration Telephone	Comment/Information Request	Clinical	

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Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	Conversation		Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Other: Status Update (Post- Marketing Commitment Request)			
22-Dec-1999	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Commitment to Conduct Studies Post Approval			
Protocol: S3B20023				
23-Dec-1999	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Commitment to conduct Phase 4 Studies			
Protocol: S3B20023				
23-Dec-1999	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Microbiology Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical, Nonclinical, Other: Post-Marketing Commitments			
05-Jan-2000	Food and Drug Administration Telephone Conversation	General Teleconference		

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Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update - Response to Proposed Labeling and Post Marketing Commitments			
07-Jan-2000	Food and Drug Administration FAX/E-mail	Comment/Information Request	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling			
07-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling, Other: Post-Marketing Commitments			
07-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling			
07-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling, Postmarketing Commitments			
10-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	CMC Labeling	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: CMC, Labeling, Other: Post Marketing Studies			
11-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference		
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference			
12-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical (Pediatric), Labeling, Other			
13-Jan-2000	Glaxo Wellcome Correspondence	General Correspondence	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Proposal for Revised Draft Labeling/Response to FDA Labeling Recommendations			
13-Jan-2000	Glaxo Wellcome Telephone Conversation	Response to FDA Request/Comment	Clinical Labeling Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical, Labeling, Safety			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
13-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Clinical			
13-Jan-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			
14-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Request Status Update Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Request Status Update (NDA Review), Safety			
17-Jan-2000	Glaxo Wellcome Correspondence	Special Safety Update		
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Safety Update Response to FDA Request/Comment (Final Report for Study S3BA3003)			
Protocol: S3BA3003				
18-Jan-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Additional Phase IV Commitments			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
18-Jan-2000	Food and Drug Administration Correspondence	Comment/Information Request	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Commitment to Post-Approval Studies			
18-Jan-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	CMC	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: CMC			
19-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	BA/BE CMC Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: NDA Review Status Update: BA/BE, CMC, Labeling, Other			
Protocol: S3BA3003				
20-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: NDA Review Status Update			
21-Jan-2000	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical CMC Nonclinical	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
			Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request: Commitment to Conduct Studies Post Approval; Agreement to Change in Drug Product Specifications			
21-Jan-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Clinical CMC Nonclinical Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Commitment to Conduct Studies Post Approval.			
25-Jan-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update: NDA Review Activities; Labeling Negotiations			
27-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Request Status Update			
27-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Request Status Update			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
28-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Other	
		Response to FDA Request/Comment	Clinical Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Other: NDA Review Status			
31-Jan-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			
01-Feb-2000	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Other: Financial Disclosure Information			
01-Feb-2000	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Financial Disclosure Information			
01-Feb-2000	Food and Drug Administration Telephone Conversation	Comment/Information Request	Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Other: Financial Disclosure			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
02-Feb-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			
02-Feb-2000	Food and Drug Administration Telephone Conversation	General Teleconference Comment/Information Request	Other Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			
02-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			
03-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling			
03-Feb-2000	Glaxo Wellcome Telephone Conversation	Response to FDA Request/Comment	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
04-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	CMC Labeling Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: CMC, Labeling, Request Status Update			
04-Feb-2000	Food and Drug Administration FAX/E-mail	Comment/Information Request	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Comment/Information Request: Labeling			
07-Feb-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			
07-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Labeling (Final Labeling Negotiations)			
Commitment: Fax labeling with final agreed changes marked. Commitment Responsibility: M Baumgartner Commitment Due Date: 07-Feb-2000				
08-Feb-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
08-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	CMC Labeling Other Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: CMC, Labeling, Other (Pediatrics), Request Status Update			
08-Feb-2000	Glaxo Wellcome FAX/E-mail	Response to FDA Request/Comment	Clinical	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3B10903, S3B10934, S3B30015, S3B30019				
09-Feb-2000	Food and Drug Administration Correspondence	Approval Letter		
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Approval Letter			
09-Feb-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Other Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other, Status Update: Labeling Request			
09-Feb-2000	Food and Drug Administration Correspondence	Approval Letter	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Approval Letter: Labeling			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
10-Feb-2000	Glaxo Wellcome Correspondence	Special Supplement: Changes Being Effected	CMC	
	NDA 21-107; LOTRONEX™ (alosetron hydrochloride) Tablets SUPAC IR: Special Supplement: Changes Being Effected in 30 Days Qualification of an Alternate Primary Packaging Site			
10-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	CMC	
	NDA 21-107; LOTRONEX™ (alosetron hydrochloride) Tablets General Teleconference: CMC			
Commitment: Submit CBE-30 Commitment Responsibility: A Mitchell Commitment Due Date: 10-Feb-2000				
10-Feb-2000	Glaxo Wellcome Correspondence	General Correspondence	CMC Field Copy	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence: CMC Field Copy			
22-Feb-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update Concerning CBE-30			
23-Feb-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets			

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	General Memorandum: Other			
23-Feb-2000	Glaxo Wellcome Telephone Conversation	General Teleconference	Clinical Labeling Other	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Clinical, Labeling, Other: Pediatrics			
Protocol: S3BA3003				
25-Feb-2000	Glaxo Wellcome Correspondence	015-Day ADR Report	Initial	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets 015-Day ADR Report: Initial			
ADR: A0108355A				
28-Feb-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update; Notification that CBE-30 submitted February 10, 2000 is approved			
02-Mar-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Labeling	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Labeling			
02-Mar-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Other Status Update	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Other			
Protocol: S3BA3003				
06-Mar-2000	Glaxo Wellcome FAX/E-mail	General Memorandum	Other Request Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Memorandum: Other - Return of Pathology Slides			
06-Mar-2000	Glaxo Wellcome Correspondence	Response to FDA Request/Comment	Clinical Efficacy Other Safety	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment: Clinical			
Protocol: S3BA3001, S3BA3002, S3BA3003				
07-Mar-2000	Food and Drug Administration Correspondence	Approval Letter		001
	NDA 21-107/S-001; LOTRONEX™ (Alosetron Hydrochloride) Tablets Approval Letter			
13-Mar-2000	Glaxo Wellcome Telephone Conversation	Response to FDA Request/Comment		
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets Response to FDA Request/Comment			
14-Mar-2000	Glaxo Wellcome Correspondence	General Correspondence	Labeling	

Application: NDA 21107; LOTRONEX™ (Alosetron Hydrochloride) Tablets
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Correspondence:Final Printed Labeling (FPL) for approved NDA 21-107.			
16-Mar-2000	Food and Drug Administration Telephone Conversation	General Teleconference	Other Status Update	
	NDA 21-107; LOTRONEX™ (Alosetron Hydrochloride) Tablets General Teleconference: Status Update: Pediatric Request, Labeling, Clinical Data			
22-Mar-2000	Glaxo Wellcome Correspondence	015-Day ADR Report	Initial	
	15-day Initial Postmarketing Reports			

EXHIBIT 9G

Document Chronology / Due Diligence Logs for

IND No. 59,496

Application: IND 59496; Alosetron Hydrochloride Oral Solution
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
17-Dec-1999	Glaxo Wellcome Correspondence	Initial Investigational New Drug Application	CMC Protocol(s) Included Study Reports	0000

IND; Alosetron Hydrochloride Oral Solution
Initial Investigational New Drug Application: CMC, Protocol(s) Included
Serial No.: 0000

Protocol with Investigator(s):
S3B10903 with:
Gregory L Kearns, Pharm.D.
Protocol with Report(s):
S3B10903 with:
NN1999/00069/00

20-Dec-1999	Glaxo Wellcome FAX/E-mail	General Memorandum	Other	

IND; Alosetron Hydrochloride Oral Solution
General Memorandum: Other

23-Dec-1999	Food and Drug Administration Telephone Conversation	General Teleconference	IND # Assigned Other	

IND 59,496; Alosetron Hydrochloride Oral Solution
General Teleconference: IND # Assigned, Other: Waiver for 30-day wait granted

Protocol: S3B10903

07-Jan-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0001

IND 59,496; Alosetron Hydrochloride Oral Solution
10-Day ADR Report: Initial
Serial No.: 0001

Protocol: S3B30012

Application: IND 59496; Alosetron Hydrochloride Oral Solution
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
ADR: A0107932A				
11-Jan-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0002
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0161 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0002 10-Day ADR Report: Initial			
Protocol: S3B30011 ADR: A0108355A				
13-Jan-2000	Food and Drug Administration Correspondence	Acknowledgement	IND # Assigned	
	IND 59,496; Alosetron Hydrochloride Oral Solution Acknowledgement: IND # Assigned			
03-Feb-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0003
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0164 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0003 10-Day ADR Report: Initial			
Protocol: S3BB3002 ADR: B0070503A				
21-Feb-2000	Glaxo Wellcome Correspondence	Protocol Amendment: New Investigator Amendment: Other	Investigator Add Change in Medical Monitor	0004
	IND 59,496; Alosetron Hydrochloride Oral Solution Protocol Amendment: New Investigator Amendment: Other, Change in Medical Monitor Serial No.: 0004			

Application: IND 59496; Alosetron Hydrochloride Oral Solution
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
Protocol: S3B10903 Protocol with Investigator(s): S3B10903 with: Jeffrey L Blumer, M.D., B. Ulysses Kwang Li, M.D. Comment: William Forbes Brodie-Brown, M.B., CH.B.				
24-Feb-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0005
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0167 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0005 10-Day ADR Report: Follow-up			
Protocol: S3B30011 ADR: A0108355A				
21-Mar-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Initial	0006
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0174 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0006 10-Day ADR Report: Initial			
Protocol: S3B20023 ADR: A0114615A				
22-Mar-2000	Glaxo Wellcome Correspondence	10-Day ADR Report	Follow-up	0007
	IND 48,487; GR68755 Tablets (alosetron hydrochloride) Serial No.: 0176 IND 59,496; Alosetron Hydrochloride Oral Solution Serial No.: 0007 10-Day ADR Report: Follow-up			
Protocol: S3B30011				

Application: IND 59496; Alosetron Hydrochloride Oral Solution
Date Range: All

Date	Communication Type	Document Type	Document Subtype	Serial / Supp #
ADR: A0107106A				

EXHIBIT 10

Patent Term Extension Calculations for

Patent Term Extension of

U.S. Patent No. 5,360,800

Express Mail Label
No. EM484297842US

Patent Term Extension Calculation for U.S. Patent No. 5,360,800

Patent Issue Date: **1 Nov 1994**

IND Effective Date of 34,672: **10 May 1990**
IND Effective Date of 39,083: **11 April 1992**
IND Effective Date of 45,128: **25 May 1994**

Period of Testing Phase:

1 Nov 94 – 31 Dec 94	=	61
1 Jan 95 – 31 Dec 95	=	365
1 Jan 96 – 31 Dec 96	=	366
1 Jan 97 – 31 Dec 97	=	365
1 Jan 98 – 31 Dec 98	=	365
1 Jan 99 – 29 Jun 99	=	180
		1702 days

IND Phase / 2 = 1702 / 2 = **851 days**

NDA Submission Date: **30 Jun 1999**
NDA Approval Date: **9 Feb 2000**

Period of Approval Phase:

30 Jun 99	=	1
1 Jul 99 – 31 Jul 99	=	31
1 Aug 99 – 31 Aug 99	=	31
1 Sep 99 – 30 Sep 99	=	30
1 Oct 99 – 31 Oct 99	=	31
1 Nov 99 – 30 Nov 99	=	30
1 Dec 99 – 31 Dec 99	=	31
1 Jan 00 – 31 Jan 00	=	31
1 Feb 00 – 9 Feb 00	=	9
		225 days

IND phase/2 + NDA phase = 851+225 = 1076

Total Patent Term Extension: **1076 days**

Patent Expiry by Terminal Disclaimer:
2 Feb 2010

Extended Expiry:

3 Feb 10 – 31 Dec 10=	332
1 Jan 11 – 31 Dec 11=	365
1 Jan 12 – 31 Dec 12=	366
1 Jan 13 – 13 Jan 13 =	13
	1076 days

Expiration + 1076-Day Patent Term Extension: **13 Jan 2013**

14 Year Cap from NDA Approval Date:

NDA Approval Date + 14 yrs=

9 Feb 00 + 14 yrs = 9 Feb 2014

14 year Patent Term Cap does not apply.